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Luminary Learnings

Diabetes

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Platelet Dysfunction in Type-2 Diabetes Mellitus

Gundu H.R. Rao

Abstract

According to the Diabetes Atlas of the World, published by the International Diabetes Federation (IDF Diabetes Atlas, 7th edn, 2015), India has currently, over 70 million subjects with type-2 diabetes and China, 110 million subjects. The number of adults estimated to be living with diabetes has reached 422 million worldwide, nearly four-fold increase from 1980 figures, according to a World Health Organization (WHO) report (2014). Non-communicable Disease Risk Factor Task Force in their article in *Lancet* (April 2016) summarize, that if the year 2000 trends in prevalence of diabetes continues, It will not be possible to reach the Millennium Goals (www.un.org/millenniumgoals) of keeping the incidence of type-2 diabetes in 2025, at the 2010 level. The collective prediction of this study group has already come true. Patients with type-2 diabetes carry an equivalent or greater cardiovascular risk to that of a non-diabetic, who has already experienced a coronary event. The risk for acute coronary event in this population seems to be 2–3 times higher than non-diabetic subjects. It is a potentially fatal, chronic disease, whose risks can be prevented by better management of known risks and lifestyle changes. Inflammation, oxidative stress, hyperglycemia, endothelial dysfunction, altered hemorheology and hyper-platelet and coagulation activation pathways, seem to contribute significantly to the clinical complications of type-2 diabetes. In this article, we provide a brief overview on, vascular dysfunction, platelet biochemistry, physiology and altered function, as it relates to the clinical complications of adult on-set diabetes.

Keywords: Diabetes, Hyperglycemia, Vascular dysfunction, Platelets physiology, Platelet dysfunction

Introduction

Number of adults with type-2 diabetes has reached 450 million worldwide and has quadrupled from 1980 to 2014. A pooled analysis of 751 population-based studies by NCD Risk Factor

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Collaboration (NCD-RisC) concludes, that with increasing population growth and ageing, if post 2000 trends in incidence of diabetes continue, the probability of meeting the global target of halting the rise in the prevalence of diabetes by 2025–2010 levels worldwide, is lower than 1% [The *Lancet* 387:1513–30, 2016]. It is a pretty dim conclusion, but is based on extensive population-based comparative studies worldwide. Most populous nations like India and China (China already has achieved that position) are competing for the number one position in terms of incidence of type-2 diabetes. According to International Diabetes Federation (www.diabetesatlas.org), India has an estimated 70 million diabetics and an equal or larger number of pre-diabetics [1, 2]. Diabetes related clinical complications includes, coronary artery disease, cerebrovascular disease, diabetic nephropathy, neuropathy and retinopathy. In our opinion, all of these clinical complications are caused by altered vascular function, including the endothelial dysfunction as well as dysfunction of circulating blood cells [3–11]. In this overview, we discuss altered function of platelets in type-2 diabetic subjects and their role in the progression of clinical complications leading to acute vascular events or end organ failure.

Over 100 years ago, Professor Bizzozero from Turin University, Italy, described the function of circulating platelets. He observed them in circulating blood of living animals and in the blood removed from the blood vessels. In well-planned experiments, he demonstrated that they were the first components of the blood, to adhere to injured blood vessel *in vivo* and *in vitro* [12]. Since that time considerable progress has been made in our understanding of how platelet works in hemostasis and thrombosis. In spite of this collective knowledge, there still exist gaps in our understanding of platelet function or dysfunction in cardiometabolic diseases. Platelets circulating in blood interact with a variety of soluble agonists, such as adenosine diphosphate (ADP), epinephrine, many insoluble cell matrix components, including fibronectin, collagen, laminin, and biomaterials used for the construction of implantable medical devices [2, 13]. They play a critical role in the recognition of vascular injury, formation of effective hemostatic plugs, retraction of clots and wound healing. When hyperactive, they can initiate events leading to many clinical complications associated with acute cardiovascular and cerebrovascular events.

Platelet Activation

Although they circulate as single entities, they can interact and form aggregates with the slightest stimulation. The degree of activation depends on the strength of the activating stimuli and the nature of the surface or the information available (sequence of amino acids) on the surface of interaction. For instance, Laminin and type 1 V collagen are major components of tumors. Platelets form a monolayer on type 1 V collagen, whereas they just anchor on laminin with minimal activation. On the other hand, metastatic tumor cells seem to be rich with fibronectin, which elicits spreading of cells. Triple-helical type-3 collagen facilitates aggregation as well as secretion of granule contents. Circulating blood has large quantities of fibrinogen, yet the platelets do not interact with soluble fibrinogen. They do not recognize the characteristic RGD (arginine, glycine, aspartic acid) sequence of amino acids on fibrinogen. However, once the glycoprotein (GP) 11b/111a receptor is activated, platelets can bind to the RGD sequence and form

aggregates. On the other hand, if the fibrinogen is bound on a surface, then the RGD sequences are exposed and are available for the GP11b/111a receptor for interaction. Similarly, at low shear rate for instance in venous circulation, thrombus will be fibrin-rich, whereas, in arterial circulation at high shear the thrombus will be platelet-rich. It is important to understand these subtle differences in the activation mechanisms, in order to develop effective anti-platelet or anti-thrombotic therapies.

Since the time O'Brien and Born described some 50 years ago, light transmission aggregometry remains the reference method for measurement of platelet function [14, 15]. Four distinct phases of activation are recognized: (1) development of stickiness; (2) shape change; (3) contraction and secretion of granule contents; (4) irreversible aggregation. The exact biochemical mechanisms involved in the first two phases of platelet activation (development of stickiness and shape change) are not known.

Major biochemical events associated with ligand binding to specific membrane associated receptors, activation of receptors, transmembrane signal transduction, formation of second messengers, cytosolic calcium mobilization, release of arachidonic acid, generation of thromboxanes, assembly of filamentous actin, contraction, secretion of granule contents and irreversible aggregation have been described by several researchers [16–25]. Vessel wall injury brings similar response in platelets. In order to arrest bleeding, platelets undergo shape change, mobilize calcium, assemble actin, and cover the injured surface and form an effective hemostatic plug (Fig. 1).

Platelet Morphology and Biochemistry

Platelets have a discoid form in their resting state. This shape helps them to circulate close to the vicinity of the vessel wall and detect areas of vascular injury. James G White a pioneer of platelet

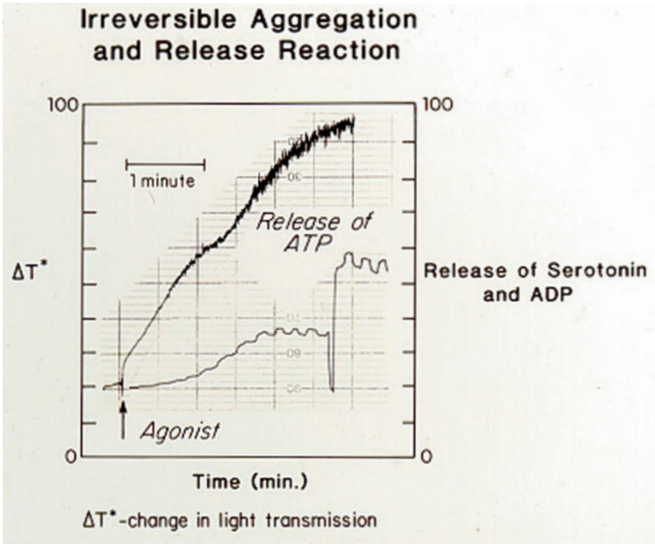

Fig. 1: Agonist induced irreversible aggregation and release of ADP and serotonin (an example of cell-cell interaction).

ultrastructure biology from University of Minnesota, has divided the platelet structure and anatomy into distinct zones. The peripheral zone consists of membranes and closely associated structures like receptors, and an exterior coat of glycocalyx, which is rich in glycoproteins. The middle layer of the peripheral zone is rich in phospholipids. More than 15% of the dry weight of platelets is lipid of which 80% is phospholipid. Major lipids include: cholesterol (30.8%), phosphatidylcholine (26.3%) phosphatidylethanolamine (8.6%), sphingomyelin (11.6%), phosphatidylserine (6.6%) and phosphatidylinositol (2.7%). In a recent study researchers at the University of Cardiff, UK, have identified over 8000 species of lipids in platelets [26]. Agonist mediated activation of platelets is associated with changes in membrane lipids, and formation of bioactive lipids (second messengers), which play an essential role in hemostasis and thrombosis.

The membrane system plays a major role in platelet physiology and function. The dense tubular system (DTS) has been shown to be the site of releasable calcium store, an important modulator of platelet activation. The DTS is also the site where enzymes involved in prostaglandin synthesis are localized [27]. The surface connected canalicular system provides access to the interior for plasma borne substances and serves as a conduit for products secreted during the release reaction [28].

Platelet plasma membranes contain transmembrane proteins as well as glycoprotein-rich domains. Glycoproteins are embedded in the lipid bilayer. Platelets contain integrin as well as non-integrin domains [29]. Integrins are transmembrane glycoproteins with alpha and beta subunits coupled non-covalently (GP11b/111a, GP1a/11a) GP1c/11a). They participate in both cell-cell and cell-matrix interactions (Fig. 2). Platelets also have non-integrin domains capable of binding other proteins such as collagen and von Willebrand Factor (GP1V, GP1b1X).

Platelet Physiology and Function

Circulating platelets interact with a variety of soluble agonists as well as cell matrix components exposed at vessel wall injury sites. These interactions stimulate specific membrane receptors and

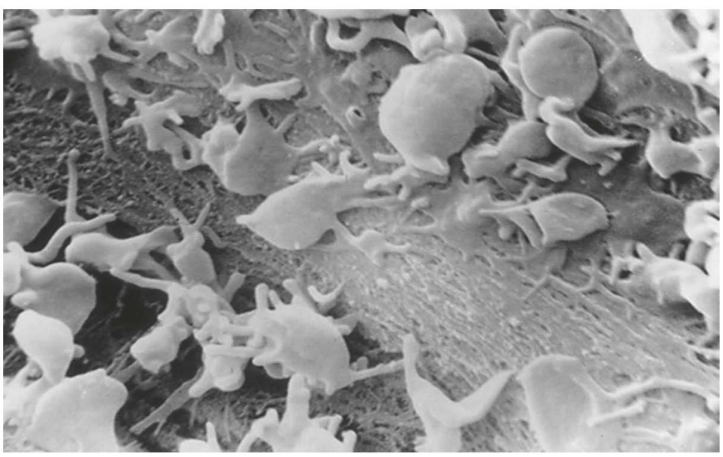

Fig. 2: Platelet interaction with blood vessel wall (cell-surface interaction) (Courtesy: James G. White).

glycoprotein-rich domains (integrin and non-integrin) on the plasma membrane and lead to the activation of intracellular enzymes [24]. The majority of cellular and molecular regulatory events seem to require participation of ionized calcium. Studies from our laboratory at the University of Minnesota, using calcium specific fluorophores (Quin-2 AM, Fura-2), demonstrated the role of ionized calcium and formation of assembled actin, in platelet activation, contraction and release reaction [30–35]. Major enzymes that regulate the free cytosolic calcium levels via second messengers include, Phospholipase C (PLC), phospholipase A_2, and phospholipase D, together with adenylyl and guanylyl cyclases (Fig. 3).

Agonist interaction with the receptor results in the activation of PLC via transmembrane signaling through hydrolysis of GTP to GDP. Platelets contain monomeric low molecular weight G proteins as well as heteromeric membrane associated G-proteins. GTP binding to the alpha subunit of G proteins facilitates the interaction with effector enzymes. Activation of PLC results in the hydrolysis of phosphatidylinositol 4,5 bisphosphate (PIP_2) and formation of second messengers, 1, 2-diacylglycerol (DAG) and 1,4,5-inositol trisphosphate (IP_3). Diglyceride activates protein kinase C (PKC), induces translocation of cytosolic PKC to membranes, whereas IP_3 mobilizes calcium from internal stores [32]. Elevated cytosolic calcium is also essential for the assembly of filamentous actin from its native soluble form. It also plays a major role in contraction and secretion of granule contents.

Elevation of cytosolic calcium activates phospholipase A_2 and liberates arachidonic acid (AA) from membrane phospholipids (Fig. 4). Free arachidonic acid is transformed by cyclooxygenase (COX) to prostaglandin (PG) endoperoxides PGG_2 and PGH_2 (Fig. 5). These transient metabolites are further transformed to thromboxane A_2 in platelets. Thromboxane is the major metabolite of this pathway and plays a significant role in platelet recruitment, granule mobilization, and secretion. Cyclic endoperoxides also are potent vasoconstrictors and potent platelet agonists.

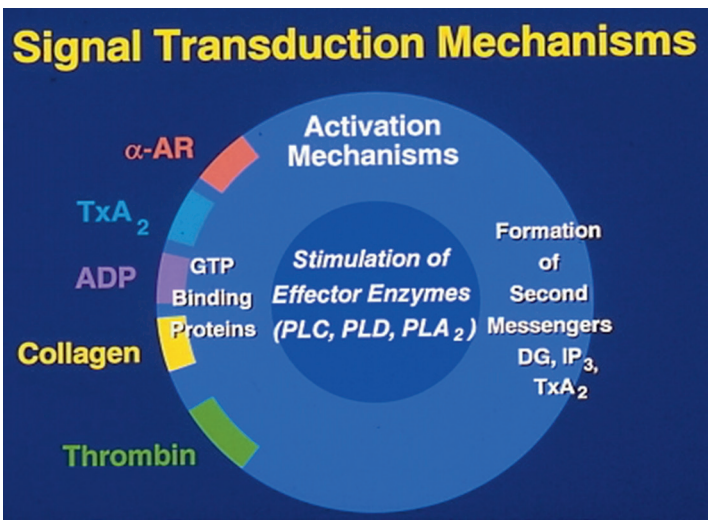

Fig. 3: Signal transduction and platelet activation mechanisms.

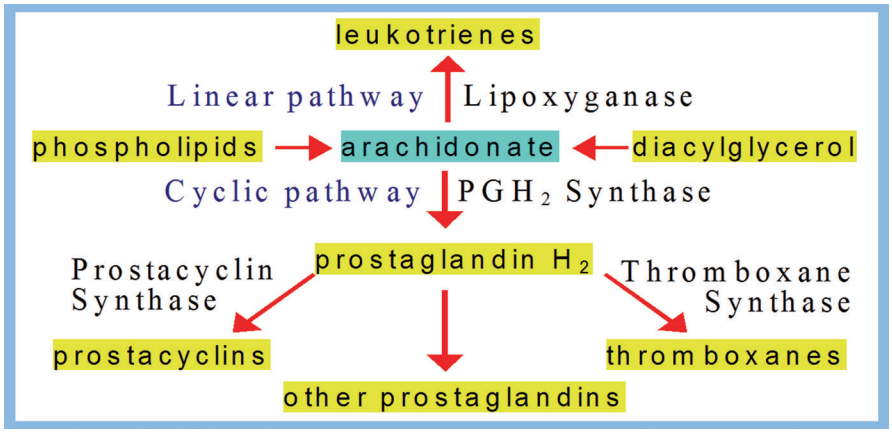

Fig. 4: Arachidonic acid metabolism by cyclooxygenase and lipoxygenase enzymes.

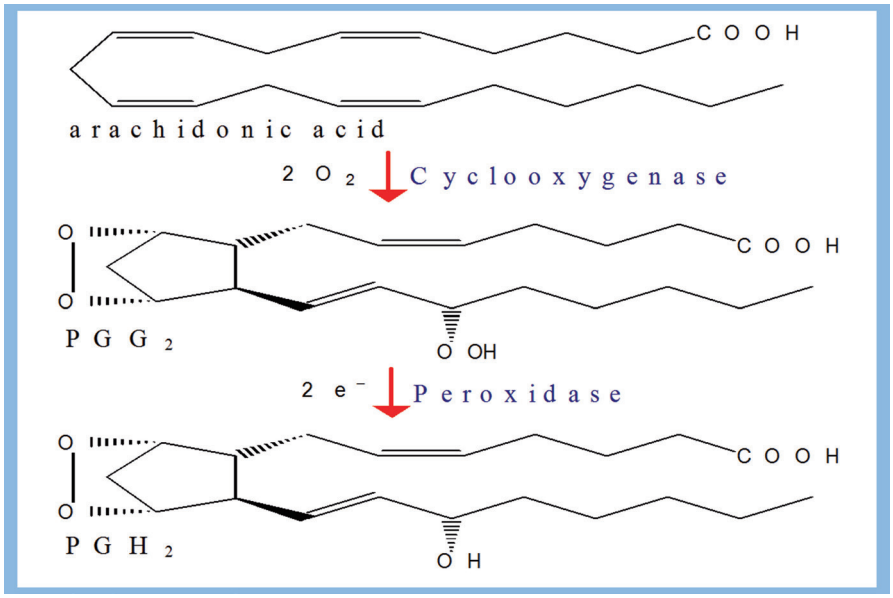

Fig. 5: Arachidonic acid metabolism by cyclooxygenase enzymes.

Similar to this metabolic pathway, the endothelial cells also generate vasoactive compounds from substrate arachidonic acid. Unlike platelets, the EC produces vasodilatory prostacyclins (PGI_2) from PG endoperoxides. These transient bioactive metabolites of AA can be utilized by platelets as well as vessel wall ECs to generate, thromboxane or prostacyclin. In view of this possibility, earlier studies focused on this aspect of cellular AA metabolism, to manage platelet hyper function, hoping that they could preferentially lower the production of proaggregatory

thromboxanes and increase the generation of vascular prostacyclin. Use of low dose aspirin and transdermal aspirin to achieve these goals, did not yield successful results.

Majority of the platelet agonists, initiate platelet activation via specific receptor mediated stimulation. Having said that, we should point out, that platelets have multiple mechanisms for activation. For instance, thrombin a protease cleaves a part of the thrombin receptor, generates thrombin receptor activation protein (TRAP), a potent agonist of platelet aggregation and promoter of release reaction. Similarly, various cell matrix components interact with specific domains on the membrane, induce platelet activation. It is generally believed, that in spite of the multiple activating mechanisms, the sequence of events that follow platelet stimulation, are common and are aimed at achieving GP11b/111a activation, fibrinogen binding, calcium mobilization, actin assembly, contraction and release of granule contents. Secretory granules contain a variety of growth factors, mitogens, and inflammatory mediators. Secretion of granules, promote expression of adhesion molecules (P-selectin) on the platelet membranes. Platelet activation also promotes expression of acidic lipids and tissue factor on the membranes, thus making these cells procoagulant. Platelet activation and changes in membrane composition promotes stimulation of prothrombinase and formation of thrombin. Fully activated platelets can activate coagulation pathways; modulate the function of other circulating blood cells such as leukocytes, monocytes, and macrophages as well as endothelial cells. Agonist induced stimulation of platelets promote the expression of an epitope on GP11b/111a receptors. Activation of this receptor is essential for the binding of circulating fibrinogen, which promotes aggregation, thrombus formation and growth [36]. von Willebrand Factor (vWF) binds platelet GP1b1X complex only at high shear rate. Unlike GP11b/111a receptor, GP1b1X receptor does not need activation to bind vWF, the globular protein changes its confirmation at high shear and binds the GP1b1X complex. Up-regulation in signaling pathways will increase the risk for clinical complications associated with acute coronary events. Down-regulation of signaling pathways may precipitate bleeding diathesis or promote hemorrhagic stroke.

Vascular Dysfunction

As mentioned earlier, we feel strongly that altered vessel wall pathology and that of blood cells play a significant role in the major clinical complications associated with the progression of type-2 diabetes. Therefore, it is important to consider not only altered blood cell physiology and function, but also the impact of vascular dysfunction. Functional and structural changes in the arterial wall precede the development of atherosclerosis, obstructive coronary artery disease, as well as serve as an early marker for hypertensive disease. Function and structural changes of vascular endothelial cells (ECs) are modulated by a variety of thrombogenic factors as well as anti-thrombogenic factors. Some of the vasoactive compounds, released by the ECs include adenosine, prostacyclin, and nitric oxide and vasoconstrictory molecules such as cyclooxygenase derived PG endoperoxides, endothelium dependent constriction factor (EDRF), hypoxia-induced endothelium dependent constriction factor. In addition, lipid peroxides, oxidized lipids, and lipoproteins promote the formation of vasoconstrictors from circulating platelets. These lipid peroxides inhibit enzymes

that promote the formation of vasodilators by the healthy endothelium and lower the production of vasodilators. Alterations in the balance between platelet associated vasoconstrictors and EC-derived vasodilators result in vascular dysfunction [4]. This is probably the earliest stage at which one can detect the manifestation of the arterial dysfunction, hypertension and atherosclerosis. One can use acetylcholine, L-arginine, or nitric oxide synthase inhibitor LNNMA and monitor the flow response to determine the degree of EC dysfunction. Alternately, one can use CV Profilor (DO-2020: Hypertension Diagnostics, Eagan Minnesota) or Periscope (Genesis Medical Systems, Hyderabad) or the system by Endothelix Inc., (Houston, Texas) for monitoring arterial stiffness. There are numerous developments in the use of ultrasound scanning technology for monitoring the progression and management of atherosclerosis [37–39].

Hemorheology and Vascular Dysfunction

Blood flow velocity and pressure in large arteries are largely influenced by the deformability of the vessel as well as the deformability of the blood cells. In addition to variety of blood constituents in the plasma (soluble and suspended), the cellular components as well as their rheological properties play major role as determinants of blood fluidity and viscosity. Red blood cells (RBCs) are major determinants of this effect. Considering the size difference in platelets and red cells (Fig. 6), any changes in membrane fluidity of the RBCs will cause obstruction in the flow of blood in the microvasculature. Therefore, deformation and orientation are the primary cellular factors affecting blood viscosity and flow velocity at high shear rates. Studies from our laboratory have developed a novel method to follow cellular deformability [40]. We have demonstrated that common drug, aspirin affects the deformability of platelet membranes and promotes adhesion of platelets to the vessel walls whereas, epinephrine reverses the effect of aspirin on platelet membranes. It is well known that the red blood cells change their shape to a parachute-like shape to move through the capillaries. Any alteration of the fluidity of cell membranes will hinder the flow of blood in microcirculation.

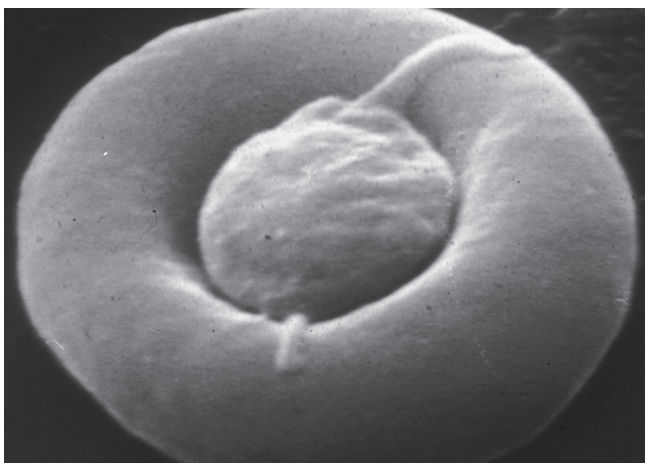

Fig. 6: Electron photomicrograph of a platelet and a red cell (courtesy: James G White).

Altered Circulating Blood Components

When we say that vascular pathology contributes significantly to the clinical complications of type-2 diabetes, it not only means the vascular dysfunction, but also includes, altered state of the circulating blood and its components. Known alterations include, inflammation, oxidative stress, elevated insulin levels, insulin resistance, elevated blood glucose, glycated or glycosylated proteins, altered vessel wall compliance, altered rheology of blood cells, imbalance in cellular activation mechanisms and coagulation pathways, changes in flow dynamics, loss of blood supply, nerve and tissue damage. Although these alterations have been reported as contributing factors to observed vascular and blood cell dysfunctions, exact role of many of these risk factors have not been validated.

Many investigators have attempted to correlate *in vitro* functional response of platelets to clinical manifestations of thrombotic or bleeding episodes. Yet, it remains a difficult task to establish a clear relationship between specific functional responses and their role in hemostasis and thrombosis. However, the presence of functional glycoprotein receptors, and the ability of the platelets to undergo shape change, become sticky, spread, irreversibly aggregate and release granule contents, are considered essential for normal hemostatic function.

Blood flow velocity and flow dynamics is a complex process, combines the fluid shearing in both the plasma and interior of red cells with elastic deformation of blood's other solid elements. As we have mentioned earlier, red cell membranes are the major contributors for this altered flow dynamics, however even platelets and other white cells also contribute to the altered flow [41, 42]. Elevated blood glucose has been shown to contribute significantly to the whole blood viscosity, erythrocyte deformability and aggregation [43]. Several researchers have demonstrated a role for altered blood and blood cell rheology in the progress of diabetic microangiopathy. They also have noted alterations in whole blood viscosity, plasma viscosity, increase in red cell 2, 3-DPG levels, elevated platelet adhesion and aggregation [44].

Infection, Inflammation and Oxidative Stress

Elevated blood glucose is the hallmark of progressive diabetic condition and this condition also supports the growth of opportunistic bacteria. It has been shown that *Mycobacterium avium* can induce apoptosis and leak of lysosomal contents and thus initiate inflammation and oxidative stress [45]. Various inflammatory diseases and soft tissue pathologies in oral cavities are associated with diabetes mellitus [46]. Studies at the University of Minnesota have demonstrated that platelet activation; aggregation and thrombosis can be initiated by platelet-associated activation protein (PAAP) expressed on oral plaque bacteria, including *Streptococcus sanguis* and *Porphyromonas gingivalis* [47, 48]. Diabetes-induced changes in immune cell function produce an inflammatory immune cell phenotype (up-regulation of pro-inflammatory cytokines from monocytes, leukocytes and down regulation of growth factors from macrophages). This predisposes to chronic inflammation, progressive tissue breakdown, and diminished tissue repair capacity [48–50]. Twin epidemics of diabetes and coronary artery disease fit the hypothesis of "common soil", when it

comes to the role of low-grade inflammation [51–53]. In view of the fact that excess weight and obesity is associated with low-grade inflammation; there is considerable interest in the role of inflammation in the pathophysiology of diabetes. Contrary to these observations, a U.S. study of adults did not show any support to the hypotheses, that inflammation is an etiologic factor for diabetes [53]. Similar to the above mentioned hypothesis, oxidative stress has been implicated as a unifying hypothesis linking various molecular disorders of type-2 diabetes [54, 55]. Studies with antioxidants like vitamin E have failed to demonstrate convincing beneficial effects of antioxidants [56]. Effect of various antioxidants needs further exploration.

Hyperglycemia and Clinical Complications of Diabetes

Chronic hyperglycemia leads to long-term macro vascular and micro vascular complications. Glycosylation refers to the covalent bonding of blood glucose to the hemoglobin of red cells [57]. Increased amount and duration of glucose in the blood allows glycosylation of not only hemoglobin, but also with other important proteins having reactive amino groups. Such glycosylation of proteins can affect cell function and structure. This condition seems to target tissues that are not dependent on insulin for their absorption of glucose (kidneys, blood vessels, peripheral nerves and lenses of the eye). Elevated glucose levels have been shown to enhance platelet activation [58]. Researchers used 5, 15 and 30 mmol/l glucose and conducted *in vitro* studies. Platelet activation was monitored by whole blood flow cytometry. Elevated levels of glucose enhanced ADP and TRAP induced expression of P-selectin as well as fibrinogen binding to platelets. Blockade of cyclooxygenase, phosphatidylinositol-3 (PI3) kinase, or nitric oxide synthase did not influence the effect of hyperglycemia. Using an *ex vivo* extracorporeal perfusion protocol, researchers monitored platelet-dependent thrombosis (PDT) in 42 patients with stable CAD [59]. Similar to the earlier studies, flow cytometry was used to monitor platelet activation. They found that PDT was significantly greater in patients with elevated blood glucose. There are several studies pointing to the ill effects of hyperglycemia and a variety of dysfunctions caused by this imbalance, however what is not clear is the exact role of hyperglycemia in the alteration of various cellular activation mechanisms and the entire coagulation pathway.

Insulin on the other hand, seems to sensitize the platelets to PGI_2 and enhance the generation of PGI_2 and nitric oxide [60]. Hyperglycemia and insulin resistance inhibit production of nitric oxide (NO) by blocking endothelial cell nitric oxide synthase (eNOS) in ECs, thereby impairing NO-mediated vasodilation, increasing production of reactive oxygen species (ROS) especially superoxide anions (O^{2-}). Superoxide quenches NO by forming toxic peroxynitrite ion, which uncouples eNOS. In addition to these mechanisms, vasoconstriction is promoted by production of angiotensin, which stimulates the generation of ROS and leads to endothelial dysfunction and inflammation.

Endothelial cells also are exposed to altered concentrations of circulating metabolites as well as glucose and therefore, are likely to be involved in the precipitation of chronic complications of the disease [61]. There is some speculation that hyperglycemia-induced polyol pathway hyperactivity associated with nerve sorbitol accumulation and myo-inositol depletion, may play a part in

the genesis of diabetic neuropathy [62]. When discussing hyperglycemia mediated dysfunctions of vascular endothelium, platelets or red cells, one should take into account that most data available are derived from experiments done in *in vitro* studies and are carried out in conditions not closely related to what is seen in *in vivo* conditions, and as such the results reported may be quite contradictory. Although we talk about glycation, glycosylation and glycosylated proteins, we do not know very much about how this process modifies the structure and function of proteins, vascular ECs and circulating blood cells. There is a great need to study the effect of hyperglycemia and hyperinsulinemia on initiation and progression of diabetes pathophysiology.

Altered Platelet Physiology and Function

Researchers from several laboratories have demonstrated hyper aggregability of platelets in response to agonists in subjects with diabetes with or without vascular disease [63–77]. The increased sensitivity to agonists is attributed to elevated levels of von Willebrand Factor (vWF). Platelets of patients with diabetes are more responsive to the arachidonic acid (AA) stimulation than platelets from normal subjects. Aspirin abolishes the increased response of platelet to AA, suggesting that cyclooxygenase metabolites of AA are responsible for increased aggregation response of platelets in diabetic subjects. They concluded that platelets of patients with diabetes have increased prostaglandin synthase activity and a PGE_2-like material was responsible for hyperactivity of platelets [63]. Gensini and associates showed that changes of platelet function in diabetics existed even in pre-diabetic conditions [66]. In view of the fact that thrombin and arachidonic acid stimulation of platelets resulted in elevated levels of malondialdehyde, they speculated increased endoperoxides-thromboxane forming activity in platelets of subjects with diabetes. They also found hypercoagulable condition in diabetics. Professor Barry Coller and associates studied diabetics with and without retinopathy and found that hemoglobin A_{1c} was elevated in all diabetic patients [67]. Whereas fibrinogen was elevated, only in diabetic subjects with retinopathy. They concluded from their studies that elevated levels of fibrinogen and vWF (promoters of venous and arterial thrombosis respectively), recognized plasma cofactors of platelet function, are associated with proliferative diabetic retinopathy. Eldor *et al*. developed a rat model for diabetes with streptozotocin and demonstrated altered platelet function and its reversal by washing the plasma off the platelet suspensions, suggesting that the components responsible for platelet hyperfunction were plasma factors [65].

Altered Eicosanoid Metabolism in Diabetes

Studies from our laboratories at the University of Minnesota demonstrated increased prostaglandin production by stimulated platelets from streptozotocin treated rats. On the other hand, the vessel wall production of prostacyclin was significantly reduced in these rats. This imbalance in the production of platelet thromboxanes and vessel wall prostacyclin was normalized by islet cell transplantation [4]. Di Mino *et al*. have suggested on the basis of their work that increased fibrinogen binding and aggregation of platelets from diabetic subjects in response to agonists is mediated

by increased formation of PGH_2 and thromboxane [71]. In spite of the fact several studies have demonstrated such altered arachidonic acid metabolism in diabetic subjects, a study from Alessandrini *et al.* could not find increased urinary metabolites of thromboxane B_2 in diabetic patients (type-1) with or without retinopathy [78]. Davi *et al.* did similar studies with type-2 diabetic subjects and as in earlier studies, did not find significant difference in urinary metabolites of thromboxane B_2 between diabetics and normal subjects. They concluded that in type-2 diabetes, increased urinary 11-dehydro-thromboxane B_2 excretion reflects enhanced biosynthesis of thromboxane A_2 by platelets, rather than a shift in its metabolic disposition [75]. Contrary to this observation, in patients with coronary artery or cerebral artery disease, researchers have found significant correlation between excess urinary metabolites of TXB_2 and risk for acute vascular events [79]. Professor Carlo Patrono and associates from Italy have described the presence of aspirin insensitive thromboxane biosynthesis under oxidant stress in severe unstable angina [80]. Since diabetics also are supposed to be under chronic oxidative stress, availability of aspirin insensitive thromboxane synthase cannot be ruled out. Several studies have reported hyperglycemia induced oxidative stress and increased production of superoxide by blood cells [82, 83].

Platelet Hypersensitivity in Diabetes

Over three decades of studies on diabetic subjects have documented a hyper aggregable state of platelets and red cells in patients with chronic diabetes mellitus. However, all attempts to make a case for infection, inflammation, oxidative stress, altered blood cell rheology, vascular dysfunction, elevated arachidonic acid metabolism, altered calcium homeostasis, expression of excess integrin receptors like GP 11b/111a and GP1b1X, to explain altered platelet function and elevated thrombotic status of blood, have failed to impress the clinicians, who have to manage this chronic disease and its clinical complications. Having said that, if we look at the way clinicians by and large treat patients with this disease, it is more or less confined to the management of blood glucose levels and in some cases hemoglobin A_{1c} (HbA_{1c}). There is still a window of opportunity to look at better management of each and every one of these risk factors. At the time of this writing, we still do not fully understand as to how exactly increased levels of blood glucose, glycation and glycosylation induce so many dysfunctions related to diabetes condition. The relationship between macroangiopathy and fasting plasma glucose or HbA_{1c} is weaker than that observed with microangiopathy. Plasma glucose or HbA_{1c} alone are unable to thoroughly explain hyperglycemia-mediated disorders of diabetes [81–83]. Several studies have reported relevance of post-prandial glucose levels as well as hyperglycemia on free radical generation and oxidative stress [81, 82]. Lipid peroxidation is an oxidative process, which occurs at relatively low levels in cells and tissues. Generation of free radicals also is a normal physiological process. To some extent these processes are regulated by the endogenous enzymatic and non-enzymatic antioxidants. Hyperglycemia mediated complications as they relate to microangiopathy may be explained to some extent by the known effect of increased blood glucose level on hemorheology. The results of Diabetes Control and Complications Trial (DCCT) in which tight control of blood glucose was one of the primary goals, reveals the beneficial effect of tight glycemic control on micro vascular health. A 10-year

follow up of over 1000 individuals, demonstrated 76% reduction in retinopathy, 50% reduction in nephropathy and 60% reduction in neuropathy [84]. In a comparative study of type-1 and type-2 diabetic patients, researchers demonstrated a relationship between the antioxidant statuses of the platelets with elevation or otherwise of eicosanoid metabolism. They found that basal thromboxane levels significantly increased in both type-1 and type-2 diabetic subjects, while malondialdehyde was increased only in type-2 subjects. Vitamin E and glutathione peroxidase activities were lower in patients with diabetes [85]. They concluded that platelet hyper activation was detectable in well-controlled diabetic patients without any clinical complications. Researchers from Belgium have studied blood levels of antioxidants, peroxides and malondialdehyde (MDA) of diabetic subjects as well as age matched healthy control subjects. In their studies they found that diabetic subjects had lower platelet glutathione and higher MDA [86]. Following this logic, Hill *et al*. from the University of Minnesota, studied the role of glutathione in platelet function and reported platelet hypersensitivity induced by 1-chloro-2,4-dinitrobenzene, hydroperoxides, inhibitors of lipoxygenase and glutathione depleting agents [87–89]. They further demonstrated, that the glutathione deficient platelets upon stimulation by arachidonic acid produce increased quantities of thromboxane and therefore, are hyperactive [89]. Radha and associates from the same group described a circadian rhythm in platelet glutathione levels [90]. Studies from the University of Minnesota on the role of glutathione inducing platelet dysfunction demonstrate, that lower antioxidant status in platelets, predisposes them to hypersensitivity to the action of arachidonic acid and promotes generation of increased quantities of PG endoperoxides. Similar studies on platelets of diabetic subjects also have shown increased level of basal Ca^{2+} (an indicator of activation), well as alteration in calcium homeostasis [91, 92].

Hyperglycemia, to a large extent exists together with hyperinsulinemia and insulin resistance in type-2 diabetes. Effect of insulin on platelet function is poorly understood. In age matched insulin resistant individuals, researchers have found increased platelet activity, suggesting that defects in insulin signal cause platelet hypersensitivity and altered calcium homeostasis [92]. Insulin is known to inhibit agonist mediated cytosolic calcium mobilization. On the other hand, epinephrine is known to enhance the sensitivity of platelet to activating agents by reducing the levels of cAMP and thereby antagonizing the effect of insulin. Elevation of plasma glucose is the main trigger for the pulsatile release of insulin to the blood. Other signals of signaling pathways that increase cytosolic calcium also release insulin. For instance the receptors coupled to heterotrimeric GTP binding proteins that stimulate PLC to produce second messengers DAG and IP3 in platelets, also can release insulin. As mentioned before, the insulin story as it relates to platelet dysfunction is poorly understood.

Now that we have briefly covered hyperglycemia, role of insulin, altered eicosanoid metabolism and platelet dysfunction, we need to discuss mechanisms independent of these established pathways of platelet activation. Studies from our laboratory using platelets devoid of dense granules, demonstrated that platelet aggregation could be achieved independent of released ADP [93, 94]. Furthermore, using platelets from patients devoid of cyclooxygenase, we demonstrated that platelet aggregation could be achieved independent of ADP or prostaglandin synthesis [95]. In view of these observations further studies were conducted to demonstrate that irreversible

aggregation could be achieved in aspirin treated platelets with epinephrine as the potentiator of agonist action [96, 97, 98]. Our studies also demonstrated that epinephrine potentiates the action of all agonists in drug-induced refractory platelets by a mechanism, described as "membrane modulation" [98]. We were able to demonstrate in a series of studies, that platelet aggregation depends upon the availability of activated GP11b/111a receptor and fibrinogen binding. We further demonstrated that so called, irreversibly aggregated platelets, could be disaggregated by using agents, which elevate AMP or cGMP and lowered cytosolic calcium [99]. These disaggregated cells could be again reaggregated, by using a combination of agents such as epinephrine and AA or epinephrine and ADP. These cycles of aggregation were accomplished by promoting fibrinogen binding to GP11b/111a receptors, phosphorylation of cytoskeletal proteins, whereas disaggregation was followed by dissociation of bound fibrinogen, dephosphorylation of cytoskeletal proteins [100].

We have earlier discussed the subtle nuances related to platelet interaction with fibrinogen. Platelets need activation of GP11b/111a receptor to find the RGD sequence and bind fibrinogen in suspension. They do not need this receptor activation, to find this sequence on fibrinogen, which is bound on a surface or on injured vessel wall. We were able to demonstrate this phenomenon in a series of experiments using denuded rabbit aorta exposed to circulating human blood. Our studies demonstrated that common anti platelet drugs inhibit cell-cell interaction (aggregate formation and thrombus growth) but not cell-surface interactions or in other words platelet vessel wall interactions [101, 102]. These studies further emphasize the complexities of platelet activation mechanisms and the difficulties one encounters in the management of platelet hyper function.

Wound Healing and Platelet Function

Platelets of type-2 diabetic subjects have been shown to be hyper sensitive to the action of agonists. Increased platelet reactivity has been attributed, to hyperglycemia, increased levels of insulin, insulin resistance, insulin deficiency, altered blood rheology, chronic inflammation, oxidative stress, endothelial dysfunction, increased expression of integrin receptors, altered arachidonic acid metabolism and platelet hyperfunction [103]. In view of these observations, explaining the role of platelets in wound healing especially in diabetic foot ulcers (DFU) becomes complicated. Studies by Knighton and associates at the University of Minnesota for the first time demonstrated, a role for platelets and platelet derived growth factor in wound healing [104, 105]. They used autologous platelet derived wound healing factors (PDWHF) from healthy subjects with non healable wounds and diabetic subjects with foot ulcers. In these studies, they demonstrated 100% healing of wounds in about 10 weeks time. Since they demonstrated that locally acting growth factors promote the healing process, these findings suggest unavailability of these factors at the site of the non-healing wound. These studies also suggest that the platelets of patients with diabetes do contain releasable platelet derived growth factors. Based on the results of these studies, one can conclude that diabetic foot ulcers are non healable because of poor circulation and lack of platelets at the wound healing sites. Indirect evidence from studies in which, ability of trans membrane delivery of nitric oxide have been shown to accelerate the healing process, also

suggests the beneficial effect of improved circulation in wound healing. Portable NO generators have been developed for therapeutic purposes (*Sci. Transl. Med.* 2015, 7:294). Yet another evidence that supports this hypothesis is the use of hyperbaric oxygen therapy for healing diabetic foot ulcers. Hyperbaric oxygen therapy is known to increase regional blood flow. Since the role of NO is well established, it is worth trying various NO generating mechanisms such as use of substrate L-arginine, or platinum nanoparticles or herbal products for wound healing applications [106, 107].

Management of Platelet Dysfunction in Diabetics

One of the major factors contributing to the increased activity of platelets in diabetics is the elevated production of platelet thromboxane. Studies of Patrignani *et al.* demonstrated selective cumulative inhibition of thromboxane production by low dose aspirin in healthy subjects [108]. They also showed that this cumulative inhibition of the platelet enzyme did not inhibit the enzymes of renal PGI_2 producing cells. Similar studies by Davi *et al.* did not show any such effect in the platelets of diabetics [77]. During the early years of eicosanoid research, there was considerable interest in the use of altered eicosanoid synthesis in the management of platelet hyper function. It was believed that one could preferentially facilitate the production of increased PGI_2 from ECs and lower the production of platelet TXA_2. Earlier studies had demonstrated that the transient endoperoxides PGG_2 and PGH_2 could be used by platelets to make TXA_2 whereas; the vessel wall ECs could use them to make PGI_2. It was speculated that a low dose of aspirin would preferentially suppress platelet production of TXA_2 and spare the COX enzymes in ECs to produce normal amounts of PGI_2.

In addition to this concept, use of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) also were recommended for the management of platelet hyper function. The idea behind this recommendation was that these fatty acids upon conversion were supposed to generate triene-Thromboxane (TXA_3) and tetraene-Thromboxane (TXA_4), instead of diene-TXA_2. Furthermore, it was speculated at that time, that the TXA of the 3 and 4 series were less potent stimulators of platelets, compared to TXA_2. Furthermore, it was speculated that the triene-PGI_3 and tetraene-PGI_4 were biologically as active as PGI_2. Studies from our laboratory demonstrated that AA is the preferred substrate for platelet COX enzymes and not much conversion of EPA and DHA occurs from platelet COX enzymes [109, 110]. Nagakawa *et al.* on the other hand, administered 2 g/per day of EPA and found increased ratio of EPA to AA in plasma and platelet phospholipids. They found a decrease in platelet aggregation following EPA consumption [111]. Terano *et al.* used purified EPA in healthy subjects and found improvement in erythrocyte deformability as well as platelet function [112]. Woodman *et al.* found highly purified DHA to be more effective anti-thrombotic agent than EPA [113]. Studies by Phang *et al.* demonstrated a differential effect of these Omega-three fatty acids on men and women tested [114]. In their studies they found that both in men and women EPA and DHA reduced platelet aggregation relative to placebo. In subgroup analyses in men, only EPA treatment reduced platelet aggregation. In contrast in women only the DHA treatment reduced platelet aggregation. In spite of these observations, clinicians do not use Omega three fatty acids as one of the anti platelet or antithrombotic therapeutic modality.

Antiplatelet Therapies

Aspirin seems to be the drug of choice for antiplatelet therapy, for both primary and secondary prevention of acute vascular events [115–117]. Those individuals who have undergone interventional procedures, such as angioplasty or coronary bypass surgery, may need dual antiplatelet therapy (combination of aspirin and clopidogrel). The American Diabetes Association (ADA) has a position statement on "Aspirin Therapy in Diabetes" [118]. According to ADA recommendations, low dose aspirin therapy should be prescribed as a secondary prevention strategy. However, they also recommend low dose aspirin for primary as well as secondary prevention in men and women with diabetes, who are at high risk for cardiovascular events. In the UK-guidelines, recommendation for diabetic patients includes treatment with aspirin (75 mg daily) or clopidogrel 75 mg/per day. Professor Belch and associates from the UK, studied the effect of aspirin and antioxidants (200 mg alpha tocopherol, 100 mg ascorbic acid, 25 mg pyridoxine hydrochloride-with small quantities of zinc sulphate, nicotinamide, selenium and lecithin) for the primary prevention in the progress of arterial disease in diabetic subjects [119]. They did not find any evidence to support the use of aspirin or antioxidants in primary prevention of acute cardiovascular events. Prof Eric Topol and associates from the U.S.A. studied the effect of aspirin alone or with clopidogrel under CAPRIE clinical trial protocol [120]. Bhat *et al*. in their report concluded (CAPRIE Trial), that the dual antiplatelet therapy was not significantly different from that of aspirin alone. Although some studies have shown that Prasugrel may be better than clopidogrel, all dual anti platelet therapies have reported increased bleeding episodes in the trial participants [120–123]. There are some reports recommending increased doses of aspirin or clopidogrel [123]. Aspirin has a very limited life in circulation. Once it is hydrolyzed to salicylic acid, metabolite salicylic acid has no inhibitory effect on COX enzymes. On the other hand, new platelets are continuously introduced into the circulation by the megakaryocytes. These newly added platelets have sufficient COX activity to generate thromboxanes capable of activating aspirin-treated-platelets [94]. In view of these observations there are some reports suggesting the use of multiple doses of low dose aspirin to lower the platelet activity. Similarly, studies have suggested increased doses of clopidogrel as well, in the management of platelet hyper activity [123]. Kokoska and associates from the U.S.A., in their most recent (2016) meta-analysis, conclude that, “It remains unclear whether aspirin may reduce the occurrence of a first atherosclerotic event or mortality in patients with diabetes” [124]. Having concluded their findings with a negative note, they suggest that more research on the use of aspirin in patients with diabetes is required. We agree with this suggestion and encourage not only further studies on aspirin use, but also the development of newer antagonists for GP11b/111a receptors.

Diabetic patients have an increased risk for atherothrombotic events as well as for end organ failure, due to the progress of microangiopathy, loss of circulation and regional ischemia. Although currently approved anti platelet and antithrombotic therapies have proven useful in improving the outcomes, diabetic patients continue to have much higher risk for acute cardiovascular and cerebrovascular events. In spite of the fact that studies after studies have suggested, that

the contributing factors for diabetes mediated clinical complications are many, the clinicians by and large concentrate on the management of blood glucose levels alone or at the most, provide minimal anti platelet therapies. Novel methods of management of this complex chronic disease should include, early detection of the risks and lowering all the well-known risk factors associated with diabetes-related clinical complications [6–11]. Major land mark trials of glycemic therapies like the DCCT of the U.S.A. and the UK Prospective Diabetes study (UKPDS), have demonstrated the beneficial effects of risk management. Studies headed by Professor Robert Turner from Oxford, unlike other clinical trials, broke many rules of clinical trial design by constant addition of further interventions and analyses. An excellent summary of this study has been provided by ADA [125]. Diabetes is a major epidemic worldwide and its clinical complications are too many to be neglected. In view of these observations an all out effort should be made, to come up with novel risk diagnosis, risk management and prevention strategies [5–11].

Conclusions

Increase in the incidence of type-2 diabetes has reached epidemic proportions worldwide, exceeding all estimations. Major contributing factors for diabetes related clinical complications include hyperglycemia, blood insulin levels, insulin resistance, inflammation, oxidative stress, changes in hemorheology, endothelial dysfunction, and platelet hyperactivity. To a great extent, all of these events are interrelated. Progression of the macrovascular disease results in increased occurrence of acute coronary or cerebrovascular events. In addition, dysfunction of the microvascular flow results in poor regional circulation or loss of circulation, ischemia and end organ failure (peripheral neuropathy, nephropathy and retinopathy). As the title of this chapter implies, platelet dysfunction plays a major role in the diabetes mediated clinical complications. Having said that, just anti platelet therapies alone, cannot solve all the problems associated with diabetes. In view of the observed clinical complications, prevention of all the major risks is the primary choice or a better choice, followed by early detection and effective management of all the known risk factors.

As part of the 2020 impact goals, the American Heart Association (AHA) has set out seven ideal health goals; not smoking, maintaining normal weight, increased physical activity, a healthy diet, normal blood lipid levels, normal blood pressure and a normal fasting glucose. An analysis of the National Health and Nutritional Examination Survey (NHANES) showed, that individuals who met five of the seven ideal metrics of AHA, had a 78% reduction in the hazard ratio for all cause-mortality [126]. From the INTERHEART study, which included 52 countries, it is estimated that modifiable risk factors account for 90% of the population attributable risk for heart disease in men and 94% of the risk in women [127]. In view of these observations, goals of our professional society, the South Asian Society on Atherosclerosis and Thrombosis (SASAT), has always been early diagnosis of the risks, effective management of the risks and prevention [128–130]. Finally, I would like to close this overview, with a statement from Professor David Katz, director of the Yale University Prevention Research Center and President of the American College of Lifestyle Medicine, "There is no pill, and there never will be any pill, that can reduce burden of chronic disease in the way that a healthy lifestyle can"(Lifestyle Interventions. Medscape Apr 22, 2105).

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2

Diabetic Retinopathy: Pathogenesis, Treatment, and Complications

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Abstract

Diabetic retinopathy is a complication of diabetes. Majority of diabetic patients with high blood glucose face the challenge of dealing with retinopathy and macular edema as the disease progresses. Although treatment choices and care are available to manage and symptomatically treat Diabetic retinopathy the current understanding is limited and lacks options for treatment and rescue strategies. Pharmacological options include anti-VEGF treatment strategies and surgical procedures. The present review provides insights in to type of diabetic retinopathy, along with different stages of the disease. In addition, the roles for health care providers, importance of pharmacists for treatment and management of diabetic retinopathy patient care are discussed.

Keywords: Diabetic retinopathy, Drug delivery, VEGF, Glucose

Introduction

Diabetic retinopathy (DR) is a complication of diabetes that affects the eyes. Diabetes affects insulin production and sensitivity and therefore the ability to absorb glucose, leading to high blood sugar levels. When blood sugar levels are high, damage can occur to the blood vessels of the light-sensitive retina, which allows for vision. For instance, high blood sugar levels can cause

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a narrowing or blockage of the retinal arteries and lead to reduced or no blood flow to the retina. As a result, endogenous processes trigger angiogenesis allowing growth of new blood vessels, but this leads to further complications. These changes to the retina affect vision and can cause blindness in diabetics.

Significance

Diabetic retinopathy holds medical, social, and economic significance. The disease affects up to 80% of people who have had diabetes for more than 20 years and accounts for 12% of all new cases of blindness. Globally, it is the leading cause of vision loss, affecting an estimated 285 million people worldwide. Recent studies have determined that about one in three people with diabetes have DR. Since it is such a prevalent health issue, the economic significance of DR is also high. In the United States alone, it is estimated that $500 million is spent on diabetes-related blindness costs. Worldwide, it is estimated that $232 billion is spent on diabetes and its complications. Given the enormous cost and financial burden that DR brings, it is essential to take measures to prevent DR, possibly by keeping good control of blood sugar levels and by early detection of eye diseases. Given the increasing prevalence of diabetes, the worldwide costs associated with it are projected to rise even more.

Studies have also been conducted to find correlations between DR and socioeconomic status. However, clear, strong relations could not be found. This weak or absent correlation can be attributed to a number of competing influences, including lifestyle, health behaviors, attitude, mortality rate, and health-care systems. For instance, a higher socioeconomic group, which receives benefits of good diabetes care and treatment, may counter those effects with a sedentary lifestyle and the consumption of western foods. This lack of correlation does not negate the importance.

There are different classifications of DR, including nonproliferative diabetic retinopathy (NPDR), proliferative DR, diabetic maculopathy, and advanced diabetic eye disease.

Patient Care Overview

Although with recent studies diabetic retinopathy (DR) and diabetes macular edema (DME) are two common ophthalmic complications for the diabetic patients, it can be kept under control through patient awareness and by adopting simple changes in lifestyle. Early detection, treatment, and improved glycemic control can limit the onset or progression of DR and DME.

The primary management for DR and DME includes three main therapies:

- Laser photocoagulation
- Intravitreal vascular endothelial growth factor (VEGF) inhibitors
- Intravitreal corticosteroid implants

Diabetic retinopathy and diabetes macular edema have multifactorial etiology due to the fact that combination therapy is gaining more popularity. Even though the change in lifestyle and

regular screening can prevent and/or reduce the effect of DR and DME, health-care providers and patient's adherence is poor and needs to be regulated with proper management. Screening and prevention goes hand in hand, and it is observed that 40% of the patients with DM and DME can prevent further ocular complications presented with their routine ocular screening. Diabetic eye exam compliance in a U.S. Medicaid population increased from 46% to 64% between 2010 and 2012. The economic cost for treating vision complication due to diabetes mellitus is estimated to be about $490 million each year indicating the burden for patients and managed care system imposed by DR and DME.

Though treatments are available to manage complications due to DR and DME, the length of the treatment causes additional burden for patients and managed care system due to necessity of longer duration of the treatment. Health plans, accountable care organizations, and other providers have more interest in investing time and proper education in ensuring their patients with diabetes (DM) receive proper vision screening and maintain adequate disease control to avoid complication due to DM which includes DR and DME. It is crucial to manage cost-effectiveness of currently available treatments of DR or DME as well as identify opportunities to improve patient adherence to treatment.

Health-care Providers and Pharmacist's Role

Encourage adherence to eye exam visits in patients with diabetes and for managing DR or DME.

Focus on Preventative Strategies

- Glycemic control
- Blood pressure control
- Lipid control
- Proteinuria and BUN/creatinine ratio

Diabetic Retinopathy and Diabetes Macular Edema Patient Education

- Increase awareness, describe risk of vision loss, explain how to prevent by addressing barriers to effective diabetes care, and use motivational interviewing.
- Lack of education – speak in layperson terms and provide reminders for routine eye exams.
- Explain therapy requirements (frequent visits), cost, and possible adverse effects.
- Monitor therapy safety and efficacy; describe what to expect with therapy, stopping vision loss, vision improvement expectations, etc.

The following simple chart can help the patient to manage DR and DME during different disease stages:

Disease stage	Presents with one of the following	Management
Early	Multiple small drusen Few medium-sized drusen Mild retinal pigment epithelial (RPE) abnormalities	Quit smoking Control body mass index (BMI) and blood pressure Increase dietary intake of antioxidants
Intermediate	Numerous medium-sized drusen At least one large druse Geographic atrophy	Keep lifestyle the same as the early disease stage Antioxidant supplements like AREDS and AREDS2
Advanced "dry" stage	Drusen with atrophy in the center of the macula	Keep lifestyle the same as the early disease stage Antioxidant supplements like AREDS and AREDS2
Advanced "wet" stage	Neovascularization with hemorrhage Lipid deposits Swelling and damage to the macula capillaries	Keep lifestyle the same as the intermediate disease stage Vascular endothelial growth factor (VEGF) inhibitors Anti-angiogenic therapy Laser therapy

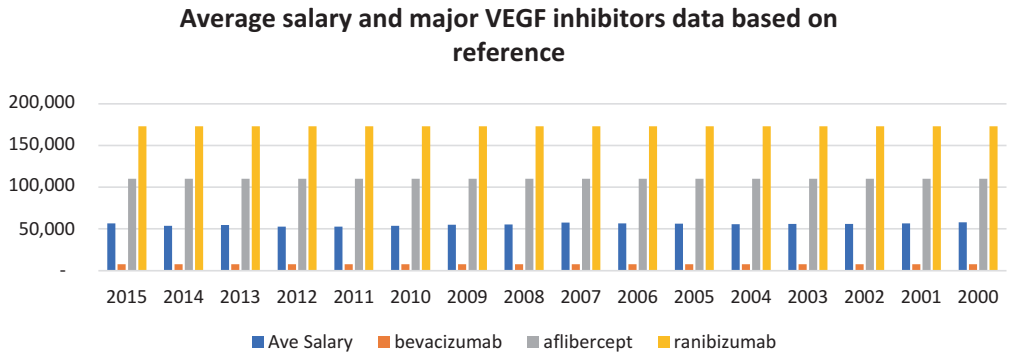
Study on Different VEGF Inhibitor Treatment Costs

In a previously published report [1], the researchers calculated the incremental cost-effectiveness ratios (ICERs) of the three drugs. One-year trial data were used to calculate cost-effectiveness for 1 year for the three anti-VEGF drugs. In addition, the researchers used mathematical modeling to project 10-year cost-effectiveness. In the patients with worse vision, 20/50 or more, aflibercept improves vision to a greater extent than bevacizumab or ranibizumab. At vision levels better than this, all drugs perform equally well.

The current study found that the more expensive agent (aflibercept) performs better in patients with worse vision. The study results also underscore the possibility of effective as-needed treatment [2]. Fixed-interval dosing would be superior to as-needed dosing. They randomly assigned participants to receive intravitreous aflibercept (2.0 mg), bevacizumab (1.25 mg), or ranibizumab (0.3 mg). Patients were treated on a needed basis as often as every 4 weeks, as opposed to on fixed dose intervals. From baseline to 1 year, the mean visual acuity letter score improved by 13.3 with aflibercept, 9.7 with bevacizumab, and 11.2 with ranibizumab. A closer examination of the data, however, revealed that the difference between the drugs was driven by improvements in eyes with worse visual acuity at baseline.

Laser photocoagulation therapy reduces risk of vision loss in patients with high-risk proliferative diabetic retinopathy and, in some cases, severe nonproliferative diabetic retinopathy.

Per Year Cost Comparison



Gaps in DR and DME Care

- Studies involving anti-VEGF therapies need to better translate to clinical practice and results be clinically significant.
- Nine injections during the first year of treatment are impractical and lead to noncompliance.
- Ability to read one additional line on an eye chart may not have meaningful functional value.
- Lack of evidence for treatment non-responders.
- Necessary DME-related services such as screening, diagnosis, treatment, and ongoing care may not be covered by insurance providers.
- Precise data on DME financial impact to individual and society are needed to justify costs advocating for improved treatment and outcomes for diabetic macular edema.

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Medscape Medical News from the Source: U.S. Census Bureau, Current Population Survey, 1968 through 2016 Annual Social and Economic Supplements.

Pathogenesis

The pathogenesis or development of DR can occur in various ways. Due to the high blood sugar levels, arterial walls of diabetics can thicken and become narrow. In the eyes, this leads to less blood flow, therefore causing DR [3]. The vascular and hematological changes of diabetic patients also lead to thickening of the capillary basement membrane, causing capillary endothelial cell damage. Red blood cells become deformed, leading to increased stickiness of platelets and increase plasma viscosity [3]. All these symptoms can in turn lead to microvascular occlusions, in which the artery leading to the eyes, the ophthalmic artery, is clamped off. This prevents bleeding and rupture. In

order to bypass this occluded artery, new arteries could grow and branch off as seen in proliferative DR. Occlusion then leads to retinal ischemia, which is the state in which blood supply to the eye is cut off [4]. The blood in the artery before the occlusion pools up, causing the artery to enlarge. This ballooning and weakened area in the artery, referred to as a microaneurysm, could rupture, leading to a hemorrhage and retinal edema. This can lead to neovascularization [4].

Factors Affecting DR

Many factors influence the likelihood and onset of DR. For instance, age and puberty significantly affect DR because of the hormonal factors responsible for growth that are involved. High levels of IGF1 and IGF2, smoking, anemia, obesity, and hyperlipidemia can all lead to the progression of DR [5]. Poor metabolic control, specifically hyperglycemia, can accentuate the progress of DR, along with ocular factors such as glaucoma, hypertension, and pregnancy [5]. DR can also be genetic, leading to increased risk of proliferative retinopathy in people with HLA DR4 and DR3 genes [5]. Whereas all of these factors increase the prevalence and likelihood of DR, myopia can decrease the prevalence and severity of retinopathy.

Different Types of DR

Nonproliferative Diabetic Retinopathy

There are two main types of DR, namely, nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy. NPDR is an early stage of DR in which tiny blood vessels within the retina leak blood or fluid, causing the retina to swell. NPDR can be characterized by microaneurysms, retinal hemorrhages, edema, hard exudates (yellowish waxy patches arranged in circinate pattern), and venous abnormalities such as beading, looping, and dilation [6]. Apart from these, NPDR can also be characterized by cotton wool spots that are small, white, superficial areas which represent areas of nerve fiber infarcts. These are a sign that the eye is not getting enough oxygen. Intraretinal microvascular abnormalities (IRMA), which are fine, irregular red lines connecting arterioles with venues representing AV shunts, are also characteristic of NPDR. NPDR can be classified into different stages, namely, mild, moderate, severe, and very severe [6].

Proliferative Diabetic Retinopathy

As the conditions of NPDR approach the severe stage, the eye may be forced to form new arteries through a process called neovascularization. This then becomes known as proliferative DR, in which new arteries form in order to bring oxygen to the hypoxic retina. Proliferative DR affects around 5–10% of the total population and develops in more than 50% of DR cases 25 years after the onset of diabetes [7]. The primary feature of PDR is neovascularization, which is caused by the angiogenic factors elaborated by the retinal tissue in an attempt to neovascularize the hypoxic retina. The angiogenic factors are most commonly the vascular endothelial growth factors (VEGF)

with isoforms like VEGF-A, VEGF-B, VEGF-C, and VEGF-D, placental growth factors, pigment epithelium-derived factors, etc. Similarly, there are several endogenous inhibitors of angiogenesis such as endostatin, platelet factor 4, and angiostatin [7]. It is hypothesized that the net balance between the VEGF and endostatin is associated with retinopathy. About one quarter of the retina has to be non-perfused before PDR develops [7].

There are two main types of proliferative DR, including PDR without high-risk characteristics and PDR with high-risk characteristics, which is also known as advanced PDR. The high-risk characteristics include neovascularization of the disc (NVD) to one fourth of the disc area, less than one fourth of the disc area, or more than half of the disc area with vitreous hemorrhage (VH) or preretinal hemorrhage (PRH) [7].

Further Side Effects

Diabetic Maculopathy

Diabetic retinopathy can lead to further complications of the patient, such as diabetic maculopathy and advanced diabetic eye disease. Diabetic maculopathy is a condition that arises from retinopathy [8]. It is concerned with damage to a specific part of the retina, the macula. When this swelling occurs in the central part of the retina (the macula), it is known as macular edema. Since the macula is the region of keenest vision, swelling of the macula could lead to reduced or blurred vision, whereas leakage or swelling elsewhere in the retina will usually not have too severe of an effect on vision. This swelling, or edema, occurs due to increased permeability of the retinal capillaries. Symptoms for diabetic maculopathy include trouble reading and recognizing faces in the center of your vision. There are also four different classifications of maculopathy, namely, focal exudative maculopathy, diffuse exudative maculopathy, ischemic maculopathy, and mixed maculopathy [8].

The diagnoses for clinically significant macular edema (CSME) can be made if one of the three criteria is present on slit-lamp examination within a 90D lens: thickening of hard exudates at or within 500 microns of the center of the fovea associated with adjacent retinal thickening, the retina at or within 500 microns of the center of the fovea, and development of zone of retinal thickening 1 disc diameter or larger in size at least a part of which is within 1 disc diameter of foveal center.

Treatment for diabetic maculopathy is most commonly done using laser photocoagulation [9]. One specific type of laser treatment is the focal treatment, in which burns are applied to microaneurysms and microvascular lesions located 500–3000 μm from the center of the macula. The spot size is 50–100 μm, and the exposure time is 0.1 s, with sufficient power to obtain a gentle whitening or darkening of the lesion. In another laser treatment, known as the grid treatment, burns are applied to areas of diffuse retinal thickening of more than 500 μm from the macula. The spot size is again 100 μm, and the exposure time is 0.1 s, resulting in a high-intensity burn [9].

Another treatment option apart from the laser photocoagulation is a pars plana vitrectomy [10]. Vitrectomy is a surgery to remove the vitreous gel containing retinal detachment or blood.

This procedure can give better access to the retina of the eye and can get rid of the edema. The pars plana vitrectomy is named as such since the instruments used to do the procedure go through the pars plana, or the flat portion of the ciliary body located near the point where the iris and sclera touch. This procedure is done only if severe persistent vitreous hemorrhage is present or if there is a premacular subhyaloid hemorrhage [10].

Advanced Diabetic Eye Disease

Another side effect of DR is advanced diabetic eye disease. This is characterized by vision-threatening complications in patients whose laser photocoagulation treatments have been unsuccessful or inadequate. There are many methods of diagnosis for this disease. Some characteristics used for diagnosis are persistent vitreous hemorrhage, tractional retinal detachment (caused by progressive contraction of fibrovascular membranes over areas of vitreoretinal attachment), tractional retinoschisis, and rubeosis iridis (caused by retinal ischemia) [11]. This disease can be preretinal, intragel, or both. Intragel hemorrhages take longer to clear than preretinal hemorrhages because the former result in more extensive bleeding. Patients should be warned that bleeding might be precipitated by severe exertion or straining, hypoglycemia, or direct ocular trauma. The treatment for this disease again is usually pars plana vitrectomy [10].

Treatment

Screening

Patients with DR should be screened frequently to monitor the condition of their disease. Typically, diabetics should be screened every year for symptoms of NPDR. Patients who already have moderate NPDR should be screened every 6 months to ensure that it is under control and not worsening. Patients with severe NPDR should be screened every 3 months, and patients with PDR should be screened every 2 months. Frequent screenings can be advantageous for the prevention and control of DR in diabetic patients [12].

Drug Delivery

Medical drugs can be taken to help treat DR. Delivery of drugs to the posterior eye is challenging, owing to anatomical and physiological constraints of the eye [13]. There is an increasing need for managing rapidly progressing posterior eye diseases, such as age-related macular degeneration, diabetic retinopathy, and retinitis pigmentosa. Drug delivery to the posterior segment of the eye is therefore compounded by the increasing number of new therapeutic entities (e.g., oligonucleotides, aptamers, and antibodies) and the need for chronic therapy. Currently, the intravitreal route is widely used to deliver therapeutic entities to the retina. However, frequent administration of drugs via this route can lead to endophthalmitis, increased intraocular pressure, and retinal detachment. Various controlled delivery systems, such as biodegradable and non-biodegradable

implants, liposomes, and nanoparticles, have been developed to overcome such adverse effects, with some success [13]. The periocular route is a promising alternative, owing to the large surface area and the relatively high permeability of the sclera. Yet, the blood–retinal barrier and efflux transporters hamper the transport of therapeutic entities to the retina. As such, the efficient delivery of drugs to the posterior eye remains a major challenge facing the pharmaceutical scientist [13].

The first line of drugs in the treatment of DR are anti-VEGF (anti-vascular endothelial growth factors). These drugs work by stopping a protein called vascular endothelial growth factor (VEGF), which is produced by the cells in the retina, from working. The overproduction of VEGFs has been connected to hypoxia, growth of new blood vessels, and consequently blindness. The two most widely used anti-VEGF drugs to counter this problem are bevacizumab (Avastin) and ranibizumab (Lucentis) [14, 15].

Specific Anti-VEGF Drugs

Bevacizumab, commercially known as Avastin, is a full-length, recombinant, humanized monoclonal antibody that works against all VEGF isoforms. It is used to treat eye diseases as well as a number of different cancers. It works by binding to all isoforms of VEGF-A and inhibiting their activity. The typical dose taken is 1–1.25 mg or 0.05 mL [14].

Ranibizumab, commercially known as Lucentis, is a genetically manipulated version of bevacizumab. It is a monoclonal antibody fragment (Fab) that is anti-angiogenic and has been approved to treat macular diseases and vision loss. Because it is genetically manipulated from the same parent mouse antibody as bevacizumab, its effectiveness is also similar to that of bevacizumab. The antibody works by inhibiting VEGF-A. All isoforms are also bound, including VEGF-110, a plasmin-cleaved form of VEGF165. The normal dosage of ranibizumab is 0.3–0.5 mg. Although ranibizumab has been proven to be relatively safe, some side effects may include conjunctival hemorrhage, eye pain, or intraocular inflammation [16].

Another anti-VEGF drug that is used is pegaptanib sodium, commercially known as Macugen. This is another anti-angiogenic drug, used to treat neovascular macular degeneration. It acts by binding specifically to the pathological 165 isoform of VEGF, which is the most important in angiogenesis, and blocking its actions, therefore reducing the growth of blood vessels and working to control leakage and swelling. An advantage of this drug is that it spares the normal vasculature, therefore giving it a dual mechanism of anti-angiogenesis and anti-permeability. The normal dosage is 0.3 mg or 90 μL [17, 18].

Anecortave acetate, commercially known as Retaane, is also known as an angiogenic steroid because of its functions. It inhibits the remodeling of basement membranes and extracellular matrix components in angiogenesis, as well as the expression of VEGF in smooth muscles. It can also be used to treat age-related macular degeneration and to reduce intraocular pressure. Anecortave acetate is delivered via the posterior juxtascleral depot (PJD) that delivers the drug onto the sclera near the macula. This method allows for decreased intraocular infection and retinal detachment. Retaane is typically delivered once every 6 months. Possible complications

of this drug include endophthalmitis, vitreous hemorrhage, persistent floaters, rise in IOP, retinal pigment epithelial tear, and retinal detachment [19].

Other Methods of Treatment

Although anti-VEGF drugs are the most common method of treatment for DR, there are other options as well. For example, protein kinase C is an intracellular signaling molecule, whose activation plays an important role in the development of ocular complications. PKC inhibitors can diminish blood flow related to hyperglycemia and therefore has potential use as a therapy for DR. Other methods can include the use of aldose reductase and ACE inhibitors, antioxidants such as vitamin E, and intravitreal steroids such as fluocinolone acetonide implants and intravitreal injections of triamcinolone at a 2–4 mg dosage [17].

Routes of Drug Delivery

Systemic, topical, periocular, and intravitreal routes are used to deliver pharmaceuticals to the posterior segment of the eye. The topical route has a lower bioavailability due to rapid drainage through the nasolacrimal ducts, a hydrophobic corneal epithelium, the blood–aqueous barrier, and the systemic absorption. Conversely the blood–retinal barrier (BRB) hinders the diffusion of systemically administered drugs to the posterior segment of the eye. Thus, the ideal routes of drug delivery are the periocular and the intravitreal routes.

Intravitreous injection of anti-VEGF, antibiotics, and steroids is the currently accepted route of administration to treat posterior segment diseases, such as diabetic retinopathy, age-related macular degeneration (AMD), vascular occlusions, cystoid macular edema, uveitis, viral retinitis, endophthalmitis, and retinal detachment. This enables direct application of the drug eliminating the barriers which are common with topical and systemic administration. A higher intraocular bioavailability yields more efficacious treatment of posterior segment diseases. Intravitreal injections are typically given at pars plana 3.5–4 mm posterior to the limbs. The availability of infusion devices such as insulin pumps (Fornia, Zhuhai, Guangdong, China) has also added to improve treatment modalities [17].

Periocular routes comprising of the retrobulbar, peribulbar, subtenon, and subconjunctival administration of drugs enable the molecules to be deposited on the external surface of the sclera, thus minimizing the risk of endophthalmitis and toxic retinal reactions. Of these, the subtenon route is considered to be the most effective method to treat posterior segment diseases of the eye [17].

Conclusion

Diabetic retinopathy is a widely prevalent disease and a common cause of visual loss. It can progress in the absence of symptoms, producing irreversible damage to the retina. The key to managing this ailment is realizing that prevention is better than treatment and a repeated follow-up of

these patients to detect the earliest sign of diabetic retinopathy. Interventions are most efficacious when started early in the disease, when retinal damage is minimal and clinical findings are few or absent. Periodic ophthalmoscopic examinations are essential in detecting the progression of retinopathy and development of disease characteristics which indicate a need for treatment. Regular screening examinations along with intensive control of hyperglycemia, serum lipid levels, and blood pressure not only retard the progression of DR but also contribute to reducing cardiovascular mortality.

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3

Using Continuous Glucose Monitoring for Patients with Fasting Hyperglycemia

J. Zhou

The dawn phenomenon and the Somogyi effect are two important causes of fasting hyperglycemia. With the application of continuous glucose monitoring (CGM) technology, it is possible to explore the mechanisms and clinical features of the dawn phenomenon and the Somogyi effect, which greatly improves the accurate understanding and management of the two phenomena and facilitates stable control of overall blood glucose level in patients with diabetes mellitus.

Definitions and Epidemiological Characteristics of the Dawn Phenomenon and Somogyi Effect

Definition

The concept of the dawn phenomenon was first put forward by Schmidt *et al.* [1] in 1981, when the authors observed an abnormal rise in glucose concentration at early morning and after breakfast in patients with type 1 diabetes and called it the "dawn phenomenon." In 1984, Bolli *et al.* [2] also reported this phenomenon in type 2 diabetes patients. Since then, the dawn phenomenon has gradually attracted the attention of researchers. The characteristics and definitions of the dawn phenomenon have been further elaborated. The current definition of the dawn phenomenon is the need for more insulin dosage to prevent a spontaneous rise in blood glucose levels in the predawn and dawn in patients with good glycemic control at nighttime without hypoglycemic events. In recent years, the utilization of CGM clinically has been shown to facilitate the detection of the dawn phenomenon and promote an in-depth understanding of the dawn phenomenon as well. At present, the scope of the dawn phenomenon includes hyperglycemia from early morning to before breakfast, and an abnormally high postprandial glucose excursion after breakfast is commonly referred to as the extended dawn phenomenon [3–5].

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The Somogyi effect is a rebound hyperglycemia episode following a nocturnal hypoglycemia episode as a result of excessive insulin during the nighttime. In 1959, the scientist Somogyi first proposed the concept that "hypoglycemia induced by excessive insulin dose can lead to rebound hyperglycemia" in his paper and put forward the hypothesis that "this rebound hyperglycemia is due to the regulation by hypothalamus-pituitary-adrenal axis" [6]. Subsequent studies have confirmed the existence of Somogyi effect [7–9], but at the same time, many scholars still have a skeptical attitude toward this phenomenon [10, 11]. Although both the dawn phenomenon and Somogyi effect are manifested as hyperglycemia in early morning, they differ completely from their pathogenesis to treatment. Thus, it is important to accurately identify and distinguish them (Table 1).

Table 1: Comparison of the dawn phenomenon and the Somogyi effect [4] (Reprinted from *Endokrynologia Polska*).

Features	The dawn phenomenon	The Somogyi effect
Definition	Recurring early morning hyperglycemia	Early morning hyperglycemia due to treatment with excessive amount of exogenous insulin
Cause	Decrease of insulin secretion between 03:00 a.m. and 05:00 a.m. and increase of insulin-antagonistic hormones	Nocturnal hypoglycemia due to excessive dose of insulin and hyperglycemia the next early morning due to increase of insulin-antagonistic hormones
Occurrence	Type 1 diabetes Type 2 diabetes with no insulin therapy	Type 1 diabetes Type 2 diabetes with insulin therapy
Incidence	Type 1 diabetic children—27.4%; Type 1 diabetic adults—24.1%; Type 2 diabetic adults—3%; Type 1 diabetes generally—54%; Type 2 diabetes generally—55%	Type 1 and 2 diabetic patients—12.6–67.0%; Type 1 diabetic patients—18%
Diagnosis	Measurement of the plasma glucose concentration between 03:00 a.m. and 05:00 a.m. for next several nights CGM Confirmative result: high/normal plasma glucose level	Measurement of the plasma glucose concentration between 03:00 a.m. and 05:00 a.m. for next several nights CGM Confirmative result: low plasma glucose level
Prevention/ treatment	Increase evening physical activity Increase protein-to-carbohydrate ratio in the last meal of the day Eat breakfast as usual even though the dawn phenomenon is presented Individual diet modification only if HbA_{1c} <7.0% (53 mmol/mol) Antidiabetic oral agent therapy only if HbA_{1c} <7.0% (53 mmol/mol) Long-acting insulin analogs like glargine insulin Use an insulin pump	Modify insulin dosage More protein than carbohydrates in the last meal of the day Go to bed with higher level of plasma glucose than usual Long-acting insulin analogs like glargine insulin Use an insulin pump

Epidemiological Characteristics

The exact incidences of the two phenomena are not yet clear. The incidence of Somogyi effect varies widely among studies, as previous studies have reported an incidence of approximately 12.6% in diabetic patients [12], but some scholars believe that this percentage is likely much higher up to 67% [13]. Another report suggests an incidence of Somogyi effect is about 18% in type 1 diabetes [4].

The reported incidence for the dawn phenomenon ranges from 3 to 55%, with estimated incidences of 24.1% and 27.4% in adults and children with type 1 diabetes, respectively [12, 14]. Another study showed an overall incidence of the dawn phenomenon as high as 55% in type 1 diabetes patients and as high as 54% in type 2 diabetes [15]. Generally, the common understanding on the incidence of both phenomena includes: (1) the dawn phenomenon is more common than Somogyi effect; (2) compared with adult diabetes, children with type 1 diabetes are more susceptible to the dawn phenomenon [4].

Pathogenesis of the Dawn Phenomenon and Somogyi Effect

Pathogenesis of the Dawn Phenomenon

The pathophysiological mechanisms of the dawn phenomenon are complex and not yet clear. It is believed that the dawn phenomenon is the result of decline in β-cell function, followed by increased endogenous glucose production and sustained insulin resistance in the early morning. In the early morning, the increase in insulin-antagonistic hormones such as growth hormone leads to impairment of the signal transduction of insulin system and enhanced lipolysis and further exaggerates insulin resistance and promotes endogenous glucose production (hepatic glycogenolysis, gluconeogenesis, etc.). With a weakened effect of insulin on peripheral tissues, especially at 08:00 a.m. when insulin sensitivity is the lowest through a day [16], together the above factors eventually trigger a dawn phenomenon. The mechanisms may involve the following aspects:

Growth Hormone

The role of growth hormone in the pathogenesis of insulin resistance has been widely studied [17]. Growth hormone is considered as the primary factor contributing to the dawn phenomenon in type 1 diabetes, and in type 2 diabetes, and it is the cause only secondary to insulin resistance contributing to the dawn phenomenon. In healthy individuals, growth hormone appears to be secreted in large amounts during slow-wave sleep and peaks from 12:00 a.m. to 2:00 a.m. However, it is known that growth hormone administration leads to substantial impairment of both hepatic and peripheral insulin sensitivity after a latency period of approximately 4 h in a healthy individual (from 04:00 a.m. to 06:00 a.m.) [15]. In 2013, Shih *et al.* [18] found an elevated blood glucose concentration, increased free fatty acid concentration, and decreased metabolic clearance rate of insulin (reflecting insulin sensitivity) at 16 h after treatment with exogenous growth hormone

in 15 type 2 diabetes patients, and this effect was weakened by the growth hormone antagonist octreotide. It is currently considered that growth hormone may lead to insulin resistance through the following pathways:

1. Impairment of the signal transduction system: growth hormone and insulin mediate intracellular glucose and lipid metabolism through a critical, common signal transduction pathway, that is, the insulin receptor substrate 1 (IRS-1)-phosphatidylinositol 3-kinase (PI-3 K) signaling pathway. Activation of the IRS-1/PI-3 K pathway activates their downstream protein kinase B to initiate a cascade of phosphorylation reactions that lead to cellular events such as activation of glycogen synthase and promotion of glucose transporter 4 (GLUT4) expression [19].
2. Enhanced lipolysis: in fasting state, growth hormone stimulates lipid oxidation and decomposition and then leads to intracellular accumulation of lipid metabolites, which competitively inhibit glucose uptake and glycogen synthesis.
3. Insulin-like growth factor (IGF) and insulin-like growth factor-binding protein (IGFBP): in 2010, Yagasaki *et al*. [20] found that IGFBP-1 also plays an important role in the occurrence of the dawn phenomenon. The authors divided 48 patients with type 1 diabetes into three treatment groups. The plasma glucose, IGFBP-1, and free IGF-1 levels of the patients were measured. The results showed that the serum IGFBP-1 levels were markedly increased at breakfast, and free IGF-1 levels were inversely decreased ($P < 0.05$) in patients with poor glycemic control who experienced the dawn phenomenon. In contrast, for those with good glycemic control, the serum IGFBP-1 levels remained stable in the morning. Therefore, the increase in circulating IGFBP-1 in the morning due to the waning of insulin action could be another mechanism behind the dawn phenomenon. The increase of IGBP-1 leads to reduced free IGF-1 levels and increases the growth hormone levels and may finally cause decreased insulin sensitivity and the dawn phenomenon.

Circadian Rhythm of Insulin Sensitivity

The dawn phenomenon is related to the circadian rhythm of insulin sensitivity in diabetic patients, with the lowest insulin sensitivity typically occurring at eight o'clock in the morning [4, 21, 22]. Endogenous glucose production also changes with circadian rhythmicity, reaching a peak in the early morning and dropping to a valley after noon. Diabetic patients have peak endogenous glucose 30–50% greater than that of the healthy individuals, resulting in elevated blood glucose levels [23].

Fibroblast Growth Factor 21 (FGF-21)

In 2011, Chen *et al*. [24] found that growth hormone-induced lipolysis was enhanced in FGF-21 knockout mice. FGF-21 interacts with growth hormone through the hypothalamus-pituitary-adrenal axis to regulate lipolysis and promote fasting gluconeogenesis. In the human body, circulating FGF-21 levels begin to rise at midnight, reach a peak in the early morning, and

then decline to basal concentrations early in the afternoon. The circulating FGF-21 levels display a circadian rhythm and resemble the oscillation of free fatty acids [25]. In conclusion, FGF-21 plays a regulatory role in growth hormone-induced dawn phenomenon.

Others

1. The effects of other insulin-antagonistic hormones such as glucagon, catecholamine, and cortisol might be involved. Carroll *et al.* [15] found an elevation of insulin-antagonistic hormones such as glucagon, catecholamine, and cortisol between 12:00 a.m. and 08:00 a.m., with the increases in glucagon and cortisol being the most dramatic [4].
2. Dietary factors include dinner intake (amount and time) of previous day or snacking at bedtime.
3. Treatment: inadequate use of oral hypoglycemic agents or insulin in the prevention of nocturnal hypoglycemia of previous day.

Pathogenesis of Somogyi Effect

The pathogenesis of Somogyi effect is mainly related to the body's negative feedback mechanisms. During a hypoglycemic event, the central nervous system is stimulated to send signals to mobilize the body to produce a series of responses against hypoglycemia, mainly through the following two pathways: (1) a direct hyperglycemic effect and (2) stimulation of the secretion of hyperglycemic hormone to antagonize the action of insulin and promote the ability of sympathetic nerve and adrenaline on the mobilization of stored energy. Hypoglycemia and the resultant excitation of the sympathetic system and increase in the plasma catecholamine levels can all inhibit the secretion of insulin, resulting in low insulinemia. Moreover, excitation of the sympathetic system and an increased plasma catecholamine level can promote the secretion of glucagon, thus increasing glycogen decomposition and gluconeogenesis. In hypoglycemic events, an inadequate supply of glucose can cause excitation of the sympathetic system with increased secretion of adrenocortical hormones, promoting the elevation of the cortisol level. Growth hormone secretion is also increased, which can inhibit the utilization of glucose in muscle tissue and directly promote the decomposition of lipid in adipose tissues.

Utilization of CGM for the Dawn Phenomenon and Somogyi Effect

Utilization of CGM for Distinguishing the Dawn Phenomenon and Somogyi Effect

Previously, the distinction between the dawn phenomenon and Somogyi effect was made mainly based on multiple blood glucose measurements at 03:00 a.m. to 05:00 a.m., especially in type 1 diabetes patients [12]. If the glucose levels were consistently low during this period, the Somogyi effect was probably the cause; if it was normal or elevated, the dawn phenomenon was more likely the reason. The dawn phenomenon is quantified by the absolute increase in glucose from

nocturnal nadir to pre-breakfast value [∂ glucose (∂G)], which is commonly defined as a rise in plasma glucose levels ∂G > 0.56 mmol/L (10 mg/dL) between 05:00 a.m. and 09:00 a.m. (every half hour), occurring after a growth hormone surge of ≥5 μg/L. In recent years, blood glucose excursion after breakfast, which is regarded as an extended dawn phenomenon, has also attracted more attention. The abnormal increase in blood glucose concentration after breakfast is considered as an obstacle to achieving stable glycemic control throughout the day. In 2002, Monnier *et al.* [21] measured the levels of blood glucose and insulin at four time points, namely, pre-breakfast (08:00 a.m.), at the postprandial state (11:00 a.m., 02:00 p.m.), and at the postabsorptive state (05:00 p.m.), and found that the blood glucose level at 11:00 a.m. was significantly higher than those at other time points. However, a certain cutoff point for identifying Somogyi effect has not yet been identified. Cryer, an American researcher, believed that the nocturnal glucose nadir relating to the Somogyi effect is probably between 3.8 mmol/L (which may cause the secretion of insulin-antagonistic hormones such as growth hormone, glucagon, epinephrine, and cortisol) and 3.0 mmol/L (which may cause hypoglycemic symptoms) [26].

In recent years, the application of CGM technology has allowed for visual observation of the circadian changes in blood glucose concentrations and for differentiation of the dawn phenomenon and Somogyi effect (Fig. 1). CGM techniques can be used to identify nocturnal hypoglycemia and the Somogyi effects that cannot be detected by glucose concentrations measured in venous blood samples [27, 28]. Schaepelynck-Bélicar *et al.* [28] observed the CGM data of 12 patients with poorly controlled type 1 diabetes. Prolonged overnight hyperglycemia was observed in five patients, the dawn phenomenon in four patients, and nighttime hypoglycemia in four patients. These data revealed that CGM enables the analysis of various glucose patterns from nighttime to early morning in these patients.

The ∂G value can be easily and accurately obtained by CGM for quantifying the dawn phenomenon. If nocturnal glucose readings at any time points are greater than that before breakfast, ∂G = 0, the dawn phenomenon is excluded. Currently, the dawn phenomenon is quantified by an absolute increase ∂G > 0.56 mmol/L (10 mg/dL) or by an absolute increase ∂G > 1.11 mmol/L (20 mg/dL) or a relative increase (∂G%) >6.9% [3]. In 2013, Monnier *et al.* [5] found that ∂G > 1.11 mmol/L (20 mg/dL) was the best cutoff value for quantifying in the application of CGM. The median of ∂G value and the median of inter-day difference from nocturnal glucose nadir to pre-breakfast glucose value among the 248 participants were 0.89 mmol/L and 0.83 mmol/L, respectively.

Utilization of CGM for Evaluation of the Dawn Phenomenon and Somogyi Effect

Continuous glucose monitoring technology improves the detection of asymptomatic nocturnal hypoglycemia and the Somogyi effect through whole-day glucose profiles. However, there are some doubts about the existence of Somogyi effect. Guillod *et al.* [29] and Høi-Hansen *et al.* [30] suggested that nocturnal hypoglycemia is a common phenomenon in type 1 diabetes patients based on an analysis of CGM data and that nocturnal hypoglycemia is not directly related to fasting hyperglycemia. On the contrary, nocturnal hypoglycemia is more likely to trigger morning hypoglycemia. Choudhary *et al.* [31] analyzed the CGM data of 89 patients with type 1 diabetes.

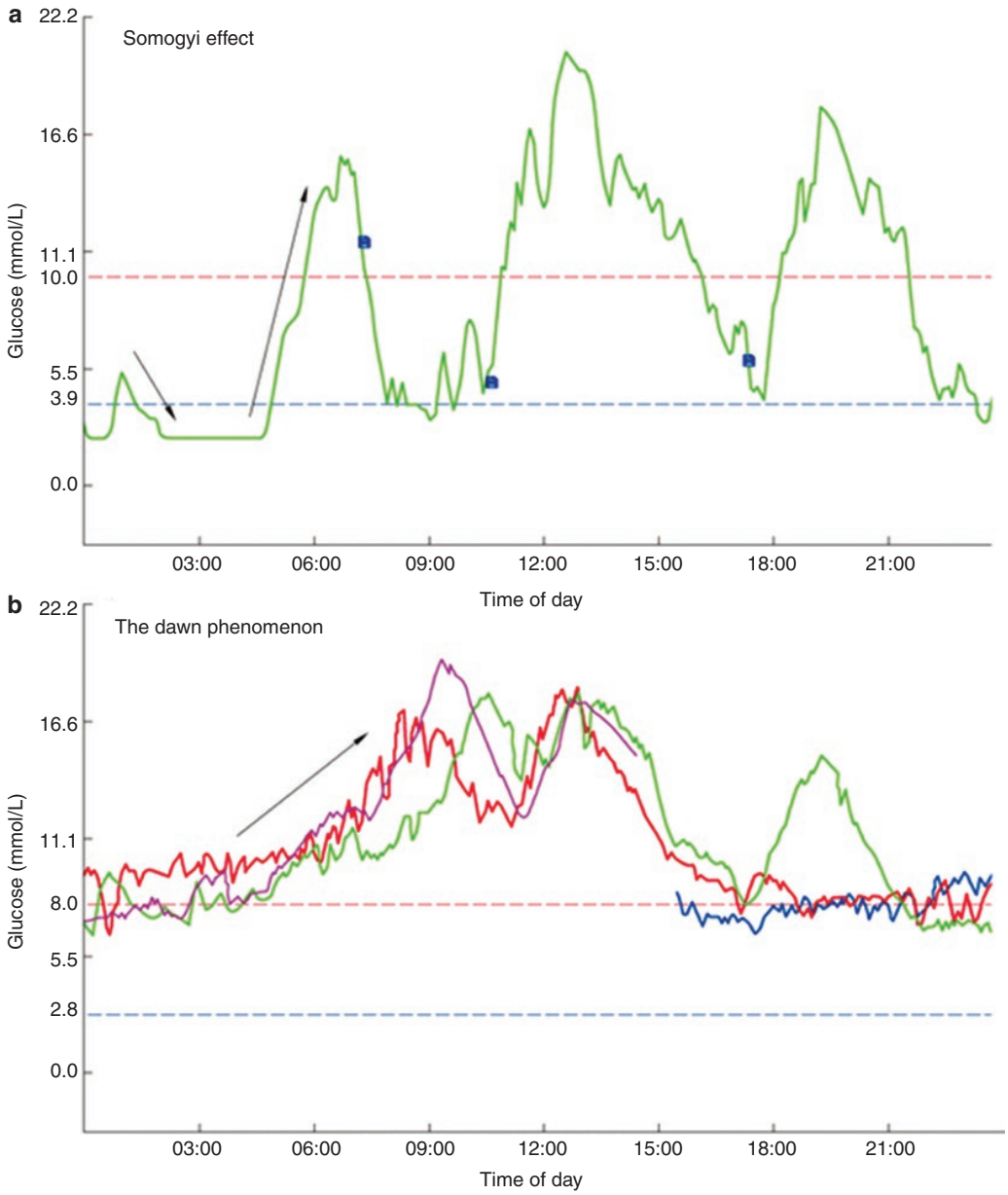

Fig. 1: CGM profiles showing the Somogyi effect (**a**) and dawn phenomenon (**b**).

They found that 94% of patients with fasting fingertip blood glucose <5 mmol/L had nocturnal hypoglycemia (defined as glucose <3.5 mmol/L), and only two subjects experienced a rebound elevation in fasting plasma glucose (FPG) after nocturnal hypoglycemia.

The existence and influence of the dawn phenomenon are well known. CGM technology promotes a better understanding of the characteristics of the extended dawn phenomenon. In 2005, Colette *et al.* [32] applied CGM in 14 type 2 diabetes on short-term calorie-restricted diet. They found that the daytime glucose peaked at 120 ± 24 min after breakfast, and there was no significant difference before and after calorie-restricted dieting. The study also found that, during periods of poor insulin sensitivity, a calorie-restricted diet failed to improve the postprandial blood glucose fluctuations, and post-breakfast was considered as the period least sensitive to caloric restriction therapy. In our previous study, 69 newly diagnosed type 2 diabetes patients and 48 normal subjects were monitored using the CGM system. The results showed that among normal subjects, the area under the curve (AUC), glucose peak value, and glucose peak time were not significantly different after meals. In type 2 diabetes, postprandial glucose fluctuations were most prominent following breakfast and less evident during lunch and dinner. The peak intraday glucose values occurred at 90 ± 37 min after breakfast, with a significantly shorter peak time than those after lunch and dinner. In addition, the peak blood glucose value after breakfast was significantly higher than those after lunch and dinner [33] (Fig. 2).

In 2013, Monnier *et al.* [5] applied CGM in 248 non-insulin-treated patients with type 2 diabetes and found that the median magnitude of the dawn glucose increase was 0.89 mmol/L and the postprandial glucose after breakfast was higher than those after lunch and dinner, emphasizing that the abnormal hyperglycemia caused by the dawn phenomenon also influences postprandial glucose after breakfast to a great extent (also called "extended dawn phenomenon").

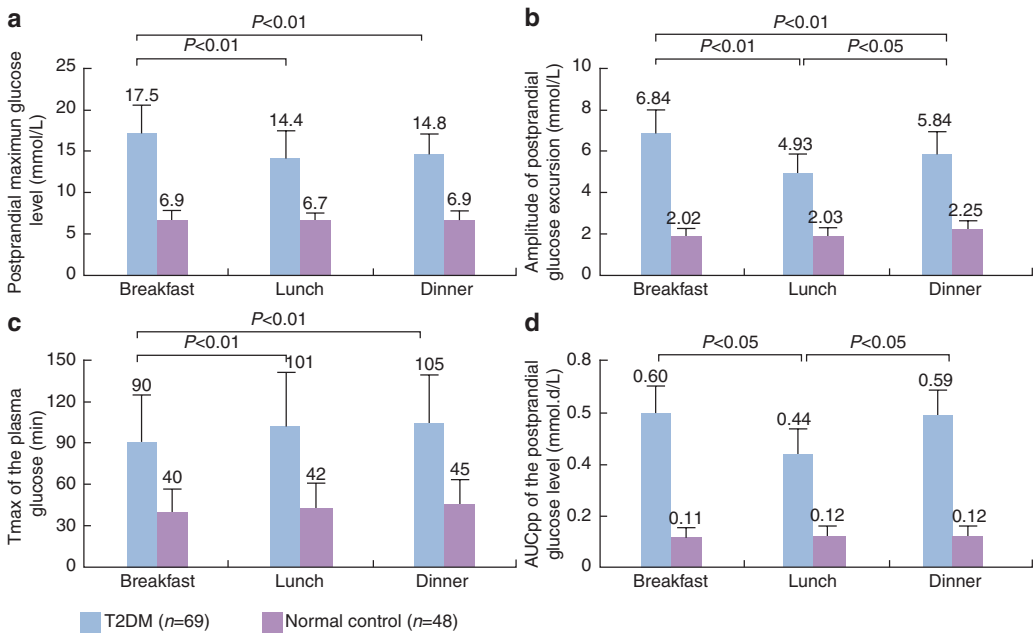

Fig. 2: The characteristics of postprandial glucose fluctuation of type 2 diabetes patients [33, 34] (Reprinted from Medical Science Monitor and reprinted with permission from *National Medical Journal of China*).

The magnitude of the dawn phenomenon is affected by the course of diabetes, glycemic control, and insulin sensitivity. In the study conducted by Perriello *et al.* [27], 114 type 1 diabetes patients were given insulin infusion, and the increased magnitude of the dawn phenomenon was associated with a short duration of diabetes, poor glycemic control, increased hepatic glucose production, and reduced peripheral glucose utilization. In addition, seven patients with poor glycemic control were selected. After 5–9 months of intensive insulin therapy, glycated hemoglobin A_{1c} (HbA_{1c}) decreased from 12.4% (112 mmol/mol) to 7.9% (63 mmol/mol) after treatment, and the magnitude of the dawn phenomenon was also decreased (evaluated by % increase between morning and nocturnal insulin requirements, 24% before treatment and 18% after treatment, $P < 0.05$). For another six poorly controlled patients without intensive insulin therapy, HbA_{1c} remained unchanged, so did the magnitude of the dawn phenomenon, during an observation period of 6–8 months. For five cases with intensive insulin therapy, the HbA_{1c} increased from 7.9% (63 mmol/mol) to 9.1% (76 mmol/mol) by 2 weeks after discontinuation of intensive treatment, and the magnitude of the dawn was also increased. These findings fully explain an intricate link between glycemic control and the magnitude of the dawn phenomenon. A similar conclusion was reached in a study of patients with type 2 diabetes. A comparison was made between morning glucose levels in seven patients with poorly controlled diabetes [HbA_{1c} 11.2% (99 mmol/mol), five type 2 and two type 1 diabetes] and levels in seven patients with well-controlled diabetes [HbA_{1c} 7.6% (60 mmol/mol), five type 2 and two type 1 diabetes]. The mean plasma glucose concentrations in the two groups increased from 6.1 mmol/L and 4.4 mmol/L at 03:00 a.m. to 12.2 mmol/L and 5.7 mmol/L at 08:00 a.m., respectively. Patients with poorly controlled diabetes exhibited a significant dawn increment in glucose levels as compared with patients with well-controlled diabetes, irrespective of the type of diabetes, suggesting that the magnitude of the dawn glucose rise was associated with glycemic control [35].

The dawn phenomenon and extended dawn phenomenon have a greater impact on blood glucose level than Somogyi effect. In the study performed by Monnier *et al.* [5], diabetic patients were divided into two groups based on the presence/absence of a dawn phenomenon (defined as $\partial G > 1.11$ mmol/L). This study was the first to investigate the impact of the magnitude of the dawn phenomenon and extended dawn phenomenon on HbA_{1c} and 24-h mean glucose in type 2 diabetes. The comparison between paired subsets of subjects for the nocturnal glucose nadir showed that the change caused by the dawn phenomenon was 0.67 mmol/L (12 mg/dL) in the mean glucose concentration and 0.4% (4 mmol/mol) in HbA_{1c}, which could not be eliminated by antidiabetic agents. These findings were consistent with the relationship previously established by the A_{1c}-Derived Average Glucose study (an increment of 1.6 mmol/L in mean glucose concentration corresponds to a 1% increment in HbA_{1c}) [36]. As another study illustrated, the deterioration of glucose homeostasis in individuals with type 2 diabetes progresses from postprandial to fasting hyperglycemia, and the dawn phenomenon state and extended dawn phenomenon are intermediate steps during the progression [37]. The morning glucose levels (pre-breakfast to 3 h after breakfast) have been found to differ significantly (7.5 mmol/L and 9.3 mmol/L, $P < 0.01$) between subjects with HbA_{1c} 6.5–6.9% (48–52 mmol/mol) and 7.0–7.9% (53–63 mmol/mol), suggesting

that the elimination of the dawn phenomenon facilitates achievement of target glycemic control [HbA_{1c} < 7.0% (53 mmol/mol)] for patients with HbA_{1c} < 8.0% (64 mmol/mol).

Utilization of CGM to Guide Treatment of the Dawn Phenomenon and Somogyi Effect

Application of CGM in diabetes can facilitate an improvement in glycemic control not only by preventing the dawn phenomenon and the occurrence of nocturnal hypoglycemia but also via timely adjustment of the treatment regimen for the dawn phenomenon and Somogyi effect. In the study conducted by Schaepelynck-Bélicar *et al.* [28], insulin treatment was adjusted based on CGM measurements in 12 adolescents with poorly controlled type 1 diabetes. The incidence of the dawn phenomenon reduced from four episodes in two patients to one episode in one patient. The mean HbA_{1c} decreased from 10.3 ± 2.1% (89 ± 23 mmol/mol) to 8.8 ± 1.1% (73 ± 12 mmol/mol). For Somogyi effect, it is important to prevent or reduce nocturnal hypoglycemia. CGM has been reported to reduce the risk of nocturnal hypoglycemia in 75% of patients [29]. CGM provides accurate data for the formulation of hypoglycemic regimen and significantly improves glycemic management. Through 24-h continuous monitoring, the CGM directly reflects the glycemic characteristics of each patient and facilitates the personalized selection of rational targeted therapies.

Principles for the Treatment of the Somogyi Effect and Dawn Phenomenon

Since the Somogyi effect is mainly due to the use of excess insulin, adjustment of insulin dose and type is first considered, e.g., replacing the neutral protamine Hagedorn (NPH) with long-acting insulin analogs (glargine or detemir insulin, etc.) [38, 39]. As an intermediate-acting insulin, NPH starts working 30–60 min after injection, peaks 4–5 h after injection, and lasts 10–16 h. The onset of action of insulin glargine is a little later than insulin NPH (1–2 h after injection), but its duration of action is 24 h. Insulin glargine or detemir acts relatively constant with no pronounced peak, which significantly reduces the risk of hypoglycemia and improves the dawn phenomenon and Somogyi effect. An insulin pump is also an effective measure to reduce the risk of nocturnal hypoglycemia. Somogyi effect may be prevented by increasing the protein-to-carbohydrate ratio in the last meal of the day, and a patient should go to bed with a reasonably high level of plasma glucose.

The essential rule for the treatment of the dawn phenomenon is to restore the normal balance of hormone in the body. Another therapeutic option is the selection of suitable hypoglycemic agents to control the morning hyperglycemia. Although some oral antidiabetic agents can improve the dawn phenomenon to varying degrees, effective control of the dawn phenomenon depends on an increase in insulin requirements at dawn. Thus, basal insulin is an optimal choice. The specific treatments are introduced as follows:

Basic Treatment

When HbA_{1c} < 7.0% (53 mmol/mol), the dawn phenomenon is generally manageable with diet and exercise therapy or combined with oral hypoglycemic agents. The dawn phenomenon may be prevented by increasing evening physical activity, increasing the protein-to-carbohydrate ratio in the last meal of the day, and eating breakfast as usual. These measures help to decrease the secretion of insulin-antagonistic hormones. In some cases, the mild dawn phenomenon can be controlled by the basic treatment combined with oral hypoglycemic agents [40].

Oral Hypoglycemic Agents

Low-dose metformin is usually used to treat the dawn phenomenon. However, it is currently believed that none of the oral hypoglycemic agents, either alone or in combination, can fully manage the dawn phenomenon. Especially, sulfonylureas are not recommended due to their potential side effect of nocturnal hypoglycemia [5].

Other medications that control the dawn phenomenon include cyproheptadine, which acts on the anterior pituitary gland to inhibit the secretion of growth hormone and adrenocorticotropic hormone (ACTH) through potent inhibitory effects against histamine and 5-hydroxytryptamine [41]. Suppression of cortisol secretion using metyrapone may also decrease the magnitude of the dawn phenomenon. In addition, administration of somatostatin can reduce FPG levels in type 1 and type 2 diabetes and resultantly decreases the magnitude of the dawn phenomenon in type 1 diabetes. However, some patients are not sensitive to this treatment. This is because somatostatin inhibits the secretion of not only glucagon and growth hormone but also insulin as well. Given that long-term inhibition of nocturnal growth hormone secretion may handicap the physical growth and development of diabetic children and adolescents, it should be used with caution clinically. The novel growth hormone antagonist pegvisomant overcomes the undesirable side effect of decreased glucose tolerance in conventional growth hormone inhibitors and provides a new direction for the treatment of the dawn phenomenon.

Insulin Therapy

Insulin should be first considered for the control of the dawn phenomenon, especially for those with HbA_{1c} >7.0% (53 mmol/mol). The latest study confirms that even in patients with HbA_{1c} <7.0% (53 mmol/mol), basal insulin therapy can reduce nocturnal hyperglycemia and the dawn phenomenon, facilitating achievement of HbA_{1c} under 7.0% (53 mmol/mol) [42, 43]. At present, the following insulin regimens are commonly used for the control of the dawn phenomenon.

Long-acting Insulin Analog at Bedtime

Compared with NPH, long-acting insulin analogs have the advantages of no significant absorption peak, lower risk of nocturnal hypoglycemia, and longer duration of action. Pistrosch *et al.*

[44] found that 36-week treatment with long-acting insulin analog at bedtime resulted in a more pronounced reduction in FPG as compared with oral administration with metformin at bedtime (Δ: 3.1 ± 2.5 mmol/L vs. 1.4 ± 1.5 mmol/L; $P < 0.001$). Both insulin glargine and detemir are basal insulin analogs. Patients treated with insulin glargine and detemir of the same dose achieve similar glycemic control with similar all-day blood glucose spectrum. Therefore, insulin glargine and detemir are capable of regulating the blood glucose level in similar ways [45, 46]. However, there is a lower glucose variability and less weight gain with insulin detemir versus insulin glargine [47, 48]. Tone *et al.* [39] found that insulin detemir versus glargine could reduce the frequency of hypoglycemia in type 1 diabetes, but not type 2 diabetic patients.

Moreover, some of the emerging drugs also provide new possibilities for the control of the dawn phenomenon. Insulin degludec (IDeg) is a new basal insulin that is ultralong-acting, which improves glycemic control to a similar degree to insulin glargine but confers lower risks of overall and nocturnal hypoglycemia [49]. In fact, the day-to-day variability in the glucose-lowering effect of IDeg is less than that for glargine, so the effect of IDeg is more predictable. The safe, predictable, and flexible profile of IDeg may be an advantage in the management of fasting hyperglycemia and nocturnal hypoglycemia [50]. Furthermore, the previous study reported that basal insulin regime changing from Lantus to Toujeo resulted in fewer hypoglycemic episodes and glucose fluctuations [51].

Insulin Pump

The insulin pump has a unique advantage in controlling nighttime and dawn blood glucose fluctuations, precisely modeling insulin secretion patterns of β-cells by adjustment of pump settings (basal rate, bolus dose). In the study conducted by Yagasaki *et al.* [20], the use of the insulin pump led to improved glycemic control from 03:00 a.m. to 07:00 a.m. and increased circulating IGFBP-1, showing the suppression of the dawn phenomenon. Papargyri *et al.* [52] reported their experience with the use of continuous subcutaneous insulin infusion (CSII) in 112 type 1 diabetes patients followed up for 7 years. They found that HbA_{1c} was reduced by 0.7–0.9% (8–10 mmol/mol) in the first 3 years, and 21% of patients had asymptomatic nocturnal hypoglycemia. The frequency of hypoglycemia decreased with the prolongation of treatment time, confirming the safety of insulin pump therapy. However, Bouchonville *et al.* [53] put forward the notion that the dawn phenomenon occurs unpredictably; therefore, programming of the insulin pump for an early morning increase in insulin delivery is ineffective for both the frequency and magnitude of the dawn phenomenon and may cause an increased risk of hypoglycemia. This defect can be avoided when applying an insulin pump with a threshold-suspend function and closed-loop insulin delivery system.

The latest study using CGM compared the efficacy of three insulin regimens, NPH (0.22 ± 0.03 U/kg), CSII (infusion of basal insulin as rapid-acting analog at single rate 0.7 ± 0.1 U/h), or long-acting insulin analogs (0.25 ± 0.02 U/kg). The results showed that bedtime NPH resulted in a magnitude of dawn phenomenon of 3.06 mmol/L, whereas CSII at single rate partly prevented the dawn phenomenon with magnitude of 0.94 mmol/L and long-acting insulin glargine eliminated the dawn phenomenon ($\partial G = 0$) [42]. Additionally, eight diabetic patients

with HbA_{1c} of 6.89 ± 0.05% (52 ± 1 mmol/mol) were treated with evening dose of insulin glargine (0.25 ± 0.02 U/kg) as add-on to metformin. After 6 months of treatment, the dawn phenomenon was basically eliminated with a decrease in the magnitude of 1.00 mmol/L; the removal of the dawn phenomenon resulted in a decrease in HbA_{1c} to 6.5 ± 0.1% (mean decrease of 0.39%) (48 ± 1 mmol/mol), which validated the estimated contribution of the dawn phenomenon to the 0.4% (4 mmol/mol) increase in HbA_{1c} calculated by Monnier *et al.* [5].

Overall, the use of long-acting insulin at a reasonable time is the most convenient and practical measure for the control of the dawn phenomenon and Somogyi effect: at 06:00 a.m. to 09:00 a.m. for reducing the risk of nocturnal hypoglycemia and improving the Somogyi effect and at 06:00 p.m. to 09:00 p.m. for preventing the dawn phenomenon.

Recently, the U.S. Food and Drug Administration (FDA) has approved the MiniMed 670G (Medtronic), a hybrid closed-loop insulin delivery system for use in patients ≥14 years old with type 1 diabetes [54]. The system uses an algorithm to automatically adjust basal insulin doses based on readings from a CGM. The new device appears to have the potential to keep blood glucose levels more stable and to improve the control of the dawn phenomenon.

Summary and Outlook

The dawn phenomenon and Somogyi effect have negative effects on the overall glycemic control of patients that cannot be ignored. The extensive application of CGM not only promotes an indepth understanding of the dawn phenomenon and Somogyi effect but also facilitates clinical identification of the two phenomena and thus improves morning glycemic control. In the future, it is necessary to further investigate their pathophysiological mechanisms, for example, the role of novel cytokines involved in particular so as to find potential targets for intervention. Also, large-scale, multicenter studies utilizing CGM technology are needed to determine the criteria for identifying the dawn phenomenon and Somogyi effect and hence further improve clinical diagnosis and treatment of these conditions.

Statement on Consent for Participation

All the clinical trials carried out by the authors in this book have been reported to the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital already and were in accordance with the Good Clinical Practice and Standards of China Association for Ethical Studies (approval number: 2007-45).

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4

Approaches to Integrated Diabetes Care: A South African Approach

Larry A. Distiller, Michael A. J. Brown

Part I: Background to the South African Health Care System

South Africa has an estimated population of 54 million people [1]. The Department of Health holds overall responsibility for healthcare, with a specific responsibility for the public sector. Because of high levels of poverty and unemployment, the bulk of the burden of healthcare is borne by the state, with 84% of the population receiving some portion of their healthcare from the public (Government) sector. Sixty-eight percent of the population does not use any private care at all, and a further 16% of the population rely on the public sector for hospital care, but use the private sector for primary care, paying out of their own pockets. Despite this burden, Government spending on healthcare comprises less than half of total health expenditure. In 2013, the remaining 16% of the population (8.64 million people) paid for private health insurance cover (often with a monthly contribution from their employers), from 87 registered medical insurance companies or medical schemes (down from 93 schemes in 2012, as schemes are battling to maintain the legislated monetary reserves and amalgamate or fold). The private sector generally supplies excellent care, but faces constant media and opportunistic political accusations of profiteering off the health burden of South Africa.

Healthcare disparities are worsened by the fact that around 70% of all doctors and most specialists only work in the private sector; the remaining 30% serve the public sector [2, 3].

A health intelligence report [4] on the future of healthcare in Africa [4], considers South Africa "by many health measures," as "the most advanced of the Sub-Saharan nations," with the biggest and most well developed, high-quality, private health insurance sector, and the largest and best-trained health workforce in Africa. It is also formulating a universal national health insurance (NHI) system, one of the first and most ambitious on the continent, in attempt to bring healthcare equality to all. However, the same report indicates that South Africa also experiences

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many healthcare problems facing other African countries, including high rates of maternal, infant and child mortality, chronic conditions including diabetes, hypertension and obesity, injuries and violence, and communicable diseases like HIV and tuberculosis. Additionally, many health services underperform on service delivery, with a background of poor management, deteriorating infrastructure, and under-funding. This has increased healthcare inequality. The private-sector health insurance system is seen as both an asset and a potential obstacle to implementing an NHI system [4]. Based on many patient reports, treatment of patients with diabetes in the public health sector is also under-resourced and underfunded. Some academic hospital diabetes clinics endeavour to provide full care, but overall, these clinics are understaffed and overextended by large patient numbers. While they do offer comprehensive diabetes education, and eye and foot screening, circumstances limit their reach and fragment their care. For example, patients verbalize that they often choose not to lose their place in 6–8 h pharmacy queues, thereby missing potentially useful consultations with dieticians and other diabetes team members.

Part II: The Growing Burden of Diabetes

Diabetes imposes a massive economic burden on all healthcare systems, accounting for 11% of total global healthcare expenditure on adults in 2013. In the next 20 years, the "developing world" is expected to be affected most by the diabetes pandemic, with 77% of people with diabetes living in low- and middle-income countries. Africa is, and will be, particularly hard-hit with 76% of deaths due to diabetes occurring in people under 60 years of age, the highest continental proportion of people with diabetes being undiagnosed (62.5%) and the largest predicted continental increase in prevalence (109.1% by 2035) [5].

With the spreading diabetes pandemic and the advent of newer, more expensive drugs to treat the condition, it can be anticipated that costs of diabetes care over the coming decades will increase incrementally. While the exact prevalence of diabetes in South Africa is unknown, the 2014 International Diabetes Federation (IDF) estimated prevalence of diabetes for South Africa was 8.39% [6], which suggests a possible total of up to 4,530,000 patients with diabetes, 737,000 in the private healthcare sector, and a further 3,800,000 in the public sector.

Worldwide funders, whether they are governments, national health services, or private health insurance companies, are desperately looking for a way to reduce costs without reducing quality of care. A number of commonly used interventions have proved to be cost-effective [7]. These include:

- The use of angiotensin-converting-enzyme inhibitors (ACE inhibitors [ACE-I]) for intensive blood pressure control
- Angiotensin-converting-enzyme inhibitor or angiotensin receptor blockers (ARB) for renal disease
- Comprehensive foot care
- Intensive risk-factor control
- Intensive insulin therapy for type 1 diabetes
- Lifestyle modification and
- Screening for and early treatment of retinopathy

While these are all important components of long-term care, the economic consequences of such treatment protocols can be overwhelming for any healthcare funder. Consequently, many funders, be they private or Government, resort to developing managed care programmes to contain costs while trying to provide quality, affordable care to their patients.

Part III: Managed Care Programmes in South Africa

Regulation 8 of the Medical Schemes Act of 1998 [8] requires South African medical schemes to pay in full for the costs of diagnosis, treatment and care of 270 medical conditions and 25 common chronic conditions, including diabetes mellitus. These "Prescribed Minimum Benefits (PMB)" are a set of defined benefits to ensure that all medical scheme members have access to certain minimum health services, regardless of the option they have chosen. "Treatment protocols" which provide guidelines for appropriate treatment for each of the chronic PMB conditions have been published in the Government gazette.

To contain the costs of providing such cover, while ensuring good quality treatment, certain measures have been taken to ensure that schemes can cover those members who need it, without putting the scheme at financial risk. Accordingly schemes are entitled to contract with "designated service providers" (specified groups of hospitals, clinics, doctors, retail pharmacies, etc.) to provide treatment for PMB conditions. However, this fact must be stated in the scheme rules and patients must be informed about where and how they can get medication and treatment from that provider. Patients who do not abide by the rules about which providers to use, may face having to pay all or part of the costs of their treatment themselves.

Often, designated service providers institute managed care programmes to standardize and control care rendered in a safe and cost-effective manner. However, many of these programmes concentrate on *cost-savings* rather than *patient service utilization* and *improved clinical outcomes.* These programmes fall into several categories:

- Programmes driven by *drug formularies,* which may exclude or restrict some more expensive and newer pharmaceutical agents. In many instances, this also extends to restricting (in patients with type 1 diabetes) or disallowing entirely (in type 2 patients) testing strips for home glucose monitoring. However, overall, the costs of medication, including insulin, accounts for just 7% of all healthcare costs related to diabetes [9].
- Programmes that *restrict the frequency of patient visits* to doctors and that *restrict access to specialist care.* The number of visits to other healthcare providers such as dietitians, podiatrists and ophthalmologists are also limited as a "cost-cutting" exercise. Not surprisingly, these funders do not even acknowledge the need for, or the role of, the Diabetes Nurse Educator and do not fund education sessions. This passes PMB muster because the "Treatment Protocols" [10, 11] focus on attainment of glycaemic targets, using mainly an algorithmic pharmacological approach, and Council for Medical Scheme PMB guidance [12] only specifies:
  - "Consultations with your treating provider (GP or specialist – if authorized by your scheme)
  - Lifestyle modification interventions such as dietary and disease education."

The type of provider is unspecified and thus the essential role of the Diabetes Nurse Educator in diabetes care [13] is ignored.

- Programmes that *restrict the number of laboratory investigations* that can be performed annually. A typical limit of services in seen in Fig. 1, as per a form sent to patients who are on this particular funders "Management Programme."
- Programmes that make use of *telephonic case manager contact* from time to time to "check how patients are doing."

While these approaches may save some costs in the short-term, managed care programmes which do not address patient outcomes nor reduce long term complications, ignore the fact that the majority of the costs for treating diabetes, even in the medium term, are due to the treatment of acute and chronic complications and for inpatient hospital care [14]. Additionally, it is well established that poor long-term clinical outcomes increase the cost burden of managing the patient with diabetes by up to 250%. Outpatient care provided in clinics or doctor's offices, accounts for less than one-quarter of the costs of accruing to a cohort of patients with diabetes [15]. Despite this, a recent study of 11 different funders in South Africa [16] showed that utilization of necessary outpatient services to monitor diabetes control and screen for potential complications is grossly inadequate. On average, only 48.37% of patients have an HbA_{1c} measured annually, 35.08% have their lipids monitored, 31.55% are tested for microalbuminuria, 20.79% see an ophthalmologist annually and 2.39% see a podiatrist (Fig. 2).

Clearly, if the economic costs of diabetes are to be contained, any approach needs to incorporate a managed care initiative that will promote better care and control of diabetes and other co-morbidities, reduce both acute and all-cause hospitalization rates, and be proactive in promoting

Tariff Code	Description	Number of Services
000192	GP - Consultation/Visit: long duration	2
000192	Specialist Consultation/Visit: long duration (Physician)	1
000192	Specialist Consultation/Visit: long duration (Ophthalmologist)	1
001232	ECG Without Effort	1
003003	Fundus contact lens or 90D lens examination	1
003009	Basic capital equipment used in Specialist rooms	1
003014	Test:Tonometry	1
004025	Blood Test: Cholesterol HDL/LDL/Trig	1
004032	Blood Test: Creatinine level	1
004050	Blood Test: Glucose Strip Test	2
004064	Blood Test: Haemoglobin A_{1C} measurement	2
004113	Blood Test: Potassium level	1
004114	Blood Test: Sodium level	1
004151	Blood Test: Urea level	1
004188	Urine Test: Dipstick	2
068302	Podiatrist Consultation 11 - 20 minutes	1
084205	Dietician Consultation	1

Fig. 1: A typical diabetes managed care programme as promoted by a medical funder.

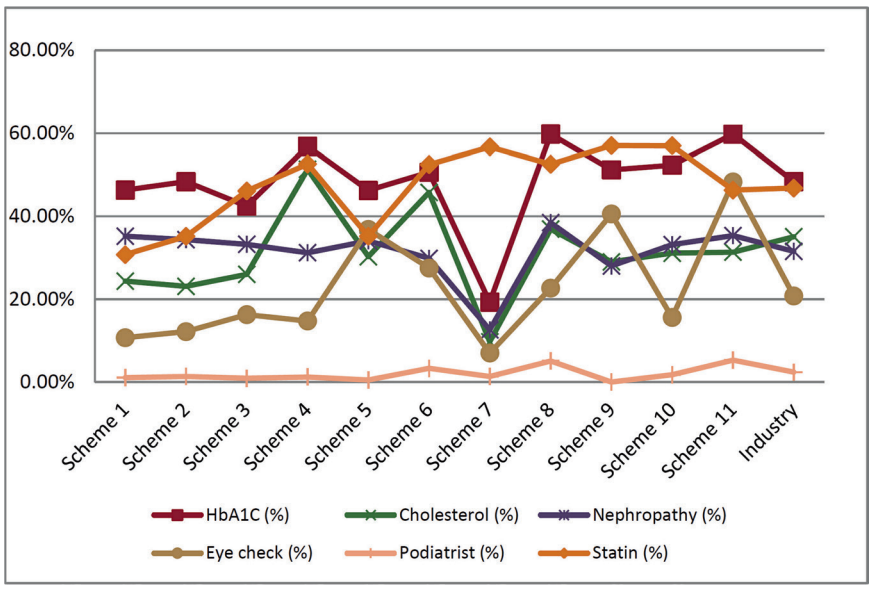


Fig. 2: Patient utilization of services across 11 medical aid schemes (funders) in South Africa (used with permission from HQA [16]).

patient health rather than reactively treating complications and problems as they arise. Most importantly, none of this will be implementable unless the system of care is designed around the *patient's perspective* of their diabetes and the needed care, the so-called "*integrated care*" of diabetes [17].

Part IV: The CDE "Diabetes Management Programme (DMP)": Past to Present

With the intensive care results and the other care insights provided by the Diabetes Control and Complications Trial (DCCT) [18], fresh in our minds, the "Centre for Diabetes and Endocrinology" was initially established as a single "Centre of Excellence" in 1994. It was staffed by two endocrinologists, two nurse educators, a registered dietician, a podiatrist, a clinical psychologist, a pharmacist and a biokineticist and effectively provided a "one-stop shop" for our patients. With all services in one place, and a well-managed appointment system, patients experienced minimal waiting and optimal consultation times. They could continue with their lives with minimal disruption. This was in stark contrast to the prevailing situation – diabetes care resources available to South Africans were generally grossly inadequate. Additionally, medical aid schemes did not appropriately fund private sector diabetes care and the resultant outcomes were generally suboptimal. We had a vision to create an all-encompassing and comprehensive diabetes treatment and management centre, which allowed us to implement correct and appropriate diabetes care principles. However, within a very short time after opening our Centre, we faced bankruptcy as the

salaries of the allied health professionals and the costs our ancillary services could only be funded from the consultation fees of the two founding medical practitioners.

We had to make a plan to survive. With our current crisis being the muse of innovation, we approached a medical aid scheme with our care offering and a simple but compelling financial equation. We knew that we could manage the monthly treatment costs of a person with diabetes for "X." We also knew that with the current hospital-centric diabetes management approaches of the time, the medical funders were paying a higher figure "Z." Could we not agree to meet somewhere in-between at a mutually agreed monthly, per patient capitation fee, "Y"? With a contractually bound promise of community-based, holistic care that prevented unnecessary hospitalization (with the Centre being responsible for the costs thereof if we failed to prevent this), our diabetes care team would receive fair professional remuneration for proactive diabetes management. The medical aid scheme would receive state-of-the art care (and improved outcomes) for their members with diabetes *and* the ability to budget for their reduced diabetes risk. This was groundbreaking thinking at that time; the concept of managed healthcare and the idea of ring-fencing, capitating and managing a condition like diabetes was alien in South Africa. In 1995, in a great leap of faith, and possibly with a glimpse into the future, this medical aid scheme contracted the services of the CDE. In the first month of operations, the CDE had 13 patients under management.

We recognized that to provide good diabetes care across South Africa, more than one "Centre of Excellence" would be required. This was also needed to meet the expectations of our first funder, which had members across South Africa. As a result, we established a founding preferred provider network of 14 CDE centres within months. At the helm at each of these initial "Centres of Excellence," was either an endocrinologist or a specialist diabetologist.

Over the past 20 years, the Centre for Diabetes and Endocrinology has expanded from these 14 centres, to a national network offering the services of 31 endocrinologists/diabetologists, 48 specialist physicians (internists), 165 "Centres of Excellence" run by trained and dedicated general practitioners and family physicians, and 610 contracted primary care doctors (Fig. 3). This network effectively offers primary, secondary and tertiary levels of expertise and care nationally in the private sector.

In tandem with the growth of the CDE provider network, the number of patients under our management has risen steadily – at the end of May 2015, our national network of 220 centres (some centres have more than one CDE-accredited doctor) were responsible for the care of 20,569 patients. Two thousand eight hundred ninety one (14.1%) had type 1 diabetes and 17,678 (85.9%), type 2 diabetes. Of the people with type 2 diabetes, 50.4% (8903) were on oral glucose-lowering agents alone and 49.6% (8775) required insulin therapy, with or without the addition of oral agents.

Persons with diabetes covered by the medical schemes and contracted to receive care via the CDE DMP encompass all of the multiple ethnic groups found in South Africa and much of the socioeconomic spectrum from blue-collar workers to company directors. We are keen to expand our best practice care to all South Africans with diabetes.

In response to the needs of funders who cannot afford the CDE traditional "Comprehensive Care Plan," from 2015 the CDE has introduced a "Standard Care Plan," which has a capitation fee

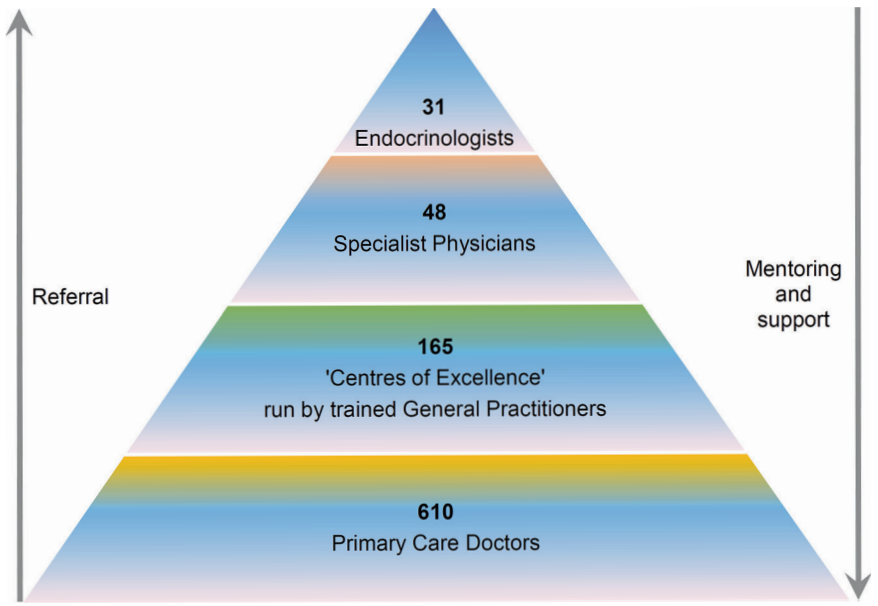


Fig. 3: The CDE network pyramid.

more palatable to funders with tight financial margins, albeit with reduced "benefits." Within this new model, payment responsibility for medicines and some services falls away from the ambit of the capitation fee. Our centres are, however, expected to refer to the core members of the diabetes team as usual, and maintain the highest possible standard of care, even though they will not be paying for all aspects directly. With this approach, we hope to enable access to improved diabetes care to many people for whom this was previously not possible. The clinical outcomes of this approach have yet to be ascertained. In this chapter, we discuss the CDE "Comprehensive Care Plan."

Part V: Structure and Principles of the CDE DMP and Diabetes Care Network

The contracted servicing doctor (Centre) receives a set monthly capitation fee, in advance, for caring for patients contracted to receive their diabetes care from that Centre. A two-tier fee structure exists, with a lower fee being paid for patients on oral glucose-lowering agents alone and a higher fee for those requiring insulin, irrespective of whether the insulin-requiring patient has type 1 or type 2 diabetes. The fee is negotiated annually based on the anticipated costs of providing all guaranteed services, plus a fair margin for the Centre taking the risk for those patients who require more intensive management, the cost of acute diabetes related hospital admissions, inflation and the choice of more expensive treatment modalities for selected patients. Centres are paid according to the number of patients they have contracted to service. Funds must be utilized

to provide all services, including clinical care, supply of all diabetes medication and accessories (including meters and testing materials for self-monitoring of blood glucose), and specified laboratory investigations (the annual measurement of lipids, renal function, and microalbuminuria is part of the guaranteed services, and careful monitoring of blood pressure is expected at every visit). Should it be found necessary, the medical scheme funds treatment for co-morbid conditions outside of the monthly capitation fee. We guarantee all medical schemes that contract the CDE Network an absolute minimum level of servicing for their patients as stated in the CDE "Minimum Care Guidelines" (Table 1). However, subjects often receive additional services in excess of these guidelines, depending on their individual clinical circumstances.

Each Centre of Excellence is required to have on staff, in addition to the responsible doctor, a trained diabetes nurse educator (DNE) to act as the primary team contact for their DMP members and to facilitate the process of patient empowerment and self-management. Each Centre must also contract with or employ both a dietitian and a podiatrist to provide the guaranteed services to the patients. For diabetes-related emergencies, every Centre must provide a direct 24-h emergency telephone number ("Hotline").

Table 1: "Minimum Care Guidelines" as contractually agreed to between CDE diabetes centres and contracted funders.

Service	Minimum frequency
Consultations:	
Doctor	2 × annually
Nurse educator	2 × annually
Dietitian (nutritional guidance)	1 × annually
Podiatrist (foot care)	1 × annually (screening)
Ophthalmologist (eye care)	1 × annually (screening)
Exercise physiologist (biokineticist)	If required
Clinical psychologist	If required
Laboratory tests to monitor diabetes:	
HbA_{1c}	6-monthly
Lipogram	1 × annually
Renal function, microalbuminuria	1 × annually
24/7/365 "Hotline" for emergencies and advice	
All diabetes medications and monitoring equipment	
Insulins and tablets	As prescribed
Blood glucose metres and test strips	As prescribed
Glucagen Hypokit	All patients on insulin therapy – replaced on use/expiry
Ketone test strips	All patients with type 1 diabetes – replaced on use/expiry
Insulin pens/syringes, needles, lancets	As prescribed

Risk assumption for hospitalization costs for acute diabetes emergencies

Via this novel diabetes-care model, CDE centres are empowered to decide on medication for the optimal treatment of their patients with diabetes – no formulary restrictions are imposed. Since each Centre must pay for the medication and insulin from the set capitation fee, the treating doctor is responsible for deciding which treatment regimen is the most cost- and quality-effective for each patient. Thus, the onus falls on the individual Centre to absorb the costs of prescribing more expensive treatment modalities should they be deemed clinically advantageous. Our centres are generally happy to do this, because they are clearly taught that the CDE DMP has an in-built level of cross subsidization (like medical aid schemes) where any available funds remaining from patients on less-expensive regimens "cover" the "deficit" accrued by patients on more expensive regimens.

Furthermore, each contracted Centre is directly responsible for all additional costs incurred should a person with diabetes under that Centre's care be admitted to hospital for a "diabetes emergency" (defined as a primary admission diagnosis of hypoglycaemia, hyperglycaemia, hyperosmolar non-ketotic coma [HONK] or diabetic ketoacidosis [DKA]). This is based on the experience that admissions for such acute metabolic events are largely avoidable in patients who have received adequate diabetes education and who are sufficiently self-empowered and have the opportunity to call their Centre via the contractually mandated 24-h emergency Hotline should they develop any acute problems. Again, our centres are happy to assume this risk (once they have a financially viable minimum of 20 capitated patients under their care), because the contracted doctors soon learn that with good care, they have the power to avoid these events. This voluntary risk assumption for the costs of hospitalization is a powerful guarantee to our funding partners that the CDE and its provider network will do the job they have contracted to do. The DMP, however, does not cover the treatment cost of any chronic complication or the treatment of other co-morbidities or risk factors, and the hospital admission costs for diabetes complications or non-diabetes-related illness. Our contracts with funders clearly state these exclusions, as the funding risk for these events would exceed the capacity of the DMP budget, which is clearly based on the *daily management costs of diabetes.*

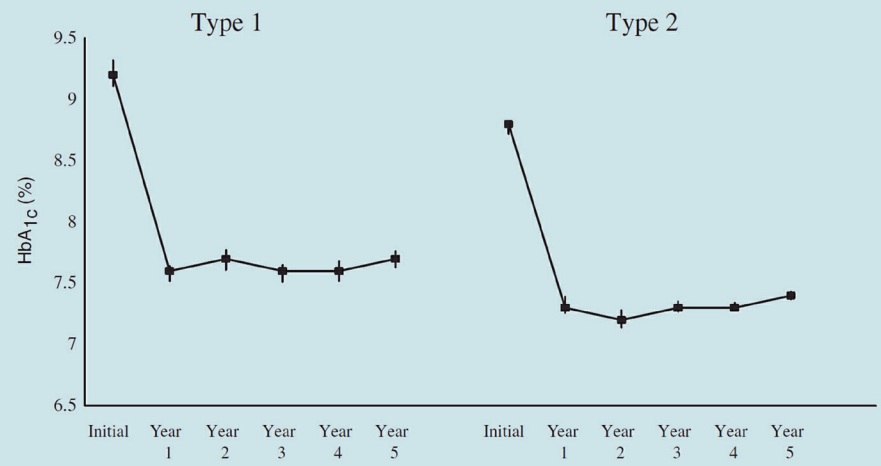
Part VI: The CDE DMP: Outcomes

Note: Since people tend to change medical schemes from time to time, with membership of the DMP depending on whether their current medical scheme was contracted to the DMP or not, long term follow-up for all patients is not always possible.

Glycaemic Control

A sustained reduction in HbA_{1c} of approximately 1.5% in subjects with both type 1 and type 2 diabetes has been achieved (Fig. 4) [19].

Although the HbA_{1c} assays were not standardized across the country, each patient had his or her HbA_{1c} performed at the same laboratory longitudinally, so that the starting HbA_{1c} for each patient effectively acted as its own control. Reasons for the sustained improvement might relate



		Initial	1 year	2 years	3 years	4 years	5 years
Type 1	Mean ±SD (%)	9.2±2.1	7.6±1.8	7.7±1.8	7.6±1.3	7.6±1.3	7.7±1.2
	Median (%)	8.9	7.4	7.5	7.4	7.5	7.5
	95% confidence limits	9.11-9.32	7.52-7.64	7.61-7.77	7.51-7.65	7.52-7.68	7.63-7.76
Type 2	Mean ±SD	8.8±1.95	7.3±1.55	7.2±1.62	7.3±1.42	7.3±1.41	7.4±1.36
	Median	8.6	7.1	7.0	7.0	7.2	7.1
	95% confidence limits	8.72-8.81	7.26-7.39	7.14-7.28	7.27-7.35	7.28-7.34	7.37-7.43

Fig. 4: Five-year follow-up of 2726 type 1 and 14,317 type 2 patients with diabetes who were part of the CDE Diabetes Management Programme for more than 5 years (used with permission from Distiller *et al.* [19]).

to the high compliance rate ensured by the CDE Programme as well as responsiveness to person-centred advice on lifestyle modification needed and an aggressive "treat-to-target" approach taught to and adopted by the CDE centres. While a mean HbA_{1c} for type 1 patients of 7.7% (±1.2% SD, Median 7.6%) after 5 years is not at the recommended target of 7%, it approaches the 7.6% suggested by the VISS (Vascular Diabetic Complications In Southeast Sweden) study to be the cut-off for the prevention of proliferative retinopathy and macroalbuminuria [20]. It is significantly better than the mean HbA_{1c} seen at many diabetes clinics, which may be in excess of 8% [21, 22]. The mean HbA_{1c} of 7.4% (±1.36% SD, median 7.1%) achieved in our type 2 patients, is considerably better than that seen in many surveys in people with type 2 diabetes including the United Kingdom Prospective Diabetes Study (UKPDS) 10-year follow-up data (mean HbA_{1c} of both the intensive and the conventional therapy groups evened out at about 8%) [23].

Hospital Admissions

Hospital admission remains the top healthcare cost in the private healthcare sector in South Africa, accounting for 39.1% of the total paid out by medical schemes in the 2013 financial

year [3]. Specifically for diabetes, the all cause hospital admission rate for patients with diabetes is threefold higher than that seen in the nondiabetic population [24]. Additionally, a study of the Economic Costs of Diabetes in the U.S. in 2012 [25] showed that for people with diabetes, hospital inpatient care accounted for 43% of the total medical cost of diabetes. Therefore, any programme that can result in even a slight reduction in the number of acute diabetes-related admissions has the potential of substantial cost savings in any healthcare system.

In this context, we have seen a significant overall reduction in all acute diabetes-related hospital admissions for patients on the CDE DMP. Our previously reported hospital admission rates [19] for patients requiring admission for acute metabolic decompensation (where the entire hospital bill was paid by their treating CDE doctor) were 6 admissions per 1000 patient-years for type 1 and 1 admission per 1000 patient-years for type 2 subjects. This was achieved with no patient mortality resulting from acute metabolic causes (hypoglycaemia, hyperglycaemia or DKA). We have had no admissions for the crisis of HONK in over 10 years, a condition that is still prevalent in many academic hospital settings [26]. Hospital admission rates for these conditions in this group of patients prior to joining the DMP were not obtainable, nor are there any published figures for hospital admissions for acute diabetes-related causes available in South Africa. The CDE DMP cohort also showed a 40% overall reduction in hospital admission rates and a 20% reduction in length of hospital stay for hospital admission diagnoses related directly or indirectly to the diabetes (acute or chronic complications). All-cause hospital admission rates were reduced from 210 admissions per 1000 patient-years for the first year on the DMP to <100 admissions per 1000 patient years in subsequent years. This reduction was sustained for the full 5 years of the study [19].

Since mortality rates were not taken into account, it could be argued that those patients with major illness or extensive arterial disease when joining the DMP could have died subsequently, leaving those in better health and with less reason for hospital admission on the Programme over subsequent years. However, the phenomenon of managed, better-controlled persons with diabetes requiring hospital admission less often than unmanaged and uncontrolled subjects is well-described. One managed care approach in Pennsylvania (U.S.A.) [27] was associated with a major reduction in the total number of admissions per patient per year, down from 0.16 to 0.12 over a 2-year period. They also documented less inpatient days and fewer emergency room visits. Another integrated diabetes disease management programme across five states in the U.S.A. also reported a 22% reduction in hospital admission rates [28] and several other studies have confirmed this [29, 30]. Attempts at an Integrated Care Initiative in the UK have been less successful [31], with an increase in hospital admission rate in the first year of the Programme, although thereafter, costs appear to have started reducing. The authors speculate that this may have been due to initial difficulties in implementing the initiative with difficulty in assuring participation of all local staff, amongst other problems.

Microvascular Disease Outcomes

Prevalence data for diabetic microvascular disease are not available for South Africa and are difficult to source internationally. The National Health and Nutrition Examination Survey (NHANES)

1999–2004 survey reported chronic kidney disease to be present in 27.8% and eye disease in 18.9% of people with diabetes in the U.S.A. [32]. Microalbuminuria was present in 20–40% of patients with diabetes [33]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reported some retinopathy in nearly all persons who had had type 1 diabetes for 20 years [34] and in nearly 80% of those who had had type 2 diabetes for the same duration [35]. Up to 21% of newly diagnosed type 2 patients have some degree of retinopathy at time of diagnosis [36]. A series of patients who were assessed for retinopathy at the time of joining the CDE DMP, showed a prevalence of 35.2% for the type 1 patients (background retinopathy 26% and referable retinopathy 9.2%) and 20.5% in the type 2 diabetes (14.1% background retinopathy and 6.4% referable retinopathy) [37]. This was in line with the internationally reported figures. In individuals who were on the CDE DMP for over 5 years, the prevalence of retinopathy was 28% for the type 1 patients and 26.6% for the type 2 patients [19]. The incidence of nephropathy (15.8% in patients with type 1 and 22.6% in patients with type 2 diabetes) was clearly lower than might have been expected for a mean duration of diabetes of 15.2 years in the type 1 group and 9.3 years for the type 2 subjects. This is probably attributable to the improved levels of glycaemic control, but also to better overall patient care and attention to and aggressive treatment of other risk factors such as hypertension and dyslipidaemia. Data on macrovascular outcomes would have been of interest, but were not sufficiently robust.

Part VII: The CDE DMP: A South African Example of Integrated Diabetes Care

The DMP has provided the CDE with over two decades of experience in many aspects of the managed care of diabetes. Our clinical outcomes include long-term improvements in glycaemic control, delay in the progression of microvascular complications and reductions in hospital admissions for both acute metabolic emergencies and all other causes.

The cost savings and resulting improvements in quality of life for the patients served are self-evident. Although no formal quality of life assessments have been performed, we have, however, been recognized for excellence in managed healthcare, by being awarded eight PMR.africa Managed Healthcare Awards since 2002 (the majority being "Diamond Arrow" Awards ranked 1st overall and rated at least 4, 10 out of 5, 00 – equivalent to outstanding). The PMR.africa awards are designed to recognize and enhance excellence in a range of industries and to set a benchmark in each sector. These externally and independently adjudicated awards are the culmination of a research process by PMR.africa, whereby companies and institutions are rated based on respondents' perceptions with a strong focus on evaluating and measuring customer service and customer satisfaction. Importantly, a company, department, institution and individual cannot "enter" the research process, but must always be nominated and rated by the respondents. In the case of managed care companies, excellence is rated by input from a random, national sample of 100 respondents (chairmen and principal officers of listed/large companies as well as fund managers, trustees, medical advisors/directors and assessors representing medical aid schemes and administrators).

Table 2: Differences between the CDE diabetes management programme and "usual" disease management programmes for diabetes.

"Usual" programmes	CDE Diabetes Management Programme
Maximum visits per year laid down	Minimum visits guaranteed. Maximum unlimited
Drug formularies	Drugs used depends only on doctor's judgement
Success measured by cost savings	Success measured by outcomes, not cost-savings
Clinical outcomes largely ignored	Clinical outcomes are key performance indicators to justify DMP existence
No transfer of risk	Risk of acute hospital admission costs transferred to provider
Task-oriented	Person-centred

Important inherent differences exist between the CDE DMP and more conventional Managed Care programmes for diabetes (Table 2). However, we believe that our focus on and attention to the provision of integrated diabetes care, since our inception, has been one of the main reasons for our many successes.

A Definition of Integrated Diabetes Care

Diabetes UK (2014) [17] offers the following definition: "Integrated care is about designing a system that focuses on the *patient's perspective of care*. The delivery of integrated care is facilitated by integration of the processes, methods and tools, which enable patients to move between services according to need. Integrated diabetes care means vertical integration between primary, community and specialist care. This is distinct from the wider agenda of horizontally integrated health and social care."

Important Patient/Provider Principles of Integrated Diabetes Care

This definition tells us that the delivery of diabetes services must be designed around the *patient's perspective of care* and the needs that accrue as a result. Diabetes mellitus is a complex, chronic, physical/psychosocial/spiritual condition that affects every part of the human experience. This gives rise to a number of challenges that we have experienced over the years, which make the understanding of the patient perspective even more important [38, 39]. Healthcare professionals (and people with diabetes) often need experience and specialized training and knowledge to achieve this mutual understanding. The resultant care principles from these insights are rolemodelled in all that we do and are included in all our healthcare-provider training courses. Once we understand these challenges and care principles, insight into the patient perspective and process of care becomes easier for all involved:

- *Chronicity*: People with diabetes battle to accept the life-long nature of their condition–in the mind of the patient, the traditional expectation of "cure" is insufficiently replaced by the

concept of a lifetime of "control" of lifestyle, blood glucose, blood pressure, serum cholesterol and body weight. Chronicity is not only a major task for the patient to deal with, but also for the *caregiver* who needs to assume a *new professional identity as a chronic care specialist.* "Treatment" of a chronic condition with a physical domain bias using an "acute-care" approach will inevitably lead to imbalance, "non-compliance" and failure to control. This can be a large spiritual, psychosocial and financial burden.

- *Change*: Diabetes is a life-changing condition. One cannot hope to facilitate the process of change (a major developmental task in diabetes) and adjust to a condition that must be mainly self-managed and that requires lifelong care and control, if one cannot identify with and manage this process oneself. This applies equally to patients and their caregivers. Change, however, is not an on-off switch, but often a long and stop-start-relapse process requiring a high degree of reflection, self-awareness, and the testing of the validity of our own attitudes, values and beliefs about something (in this case diabetes). It is these "internal" drives that determine our eventual behaviour and what our patients/clients experience as a result.
- *One size does not fit all*: One practitioner does not have the necessary knowledge and skills to treat all the different effects of diabetes. Team-facilitated management was shown in the Diabetes Control and Complications Trial (DCCT) to be a vital element in the control of type 1 diabetes by "Intensive Therapy" [40]. In addition to the doctor, input from the diabetes educator, dietitian, podiatrist, ophthalmologist, pharmacist, biokineticist and psychologist (amongst others), is necessary at different times to maximize insight, care and quality of life. The critical role of the diabetes nurse educator is reinforced by the CDE experience over the years that every CDE Centre that has won one of our eight Annual Clinical Excellence Awards, designed to recognize outstanding patient care in various categories, has had as its coordinator, an outstanding diabetes nurse educator.
- *Self-care* is vital and is a major challenge for health professionals to facilitate when they and their patients are used to conventional (acute) care approaches. The focus is on the *prevention of ill health* and *not* its treatment.
- *Continuity*: Care must be organized around a person who has a life full of events, both good and bad. The aim is to build up a coherent picture of their needs and their health status over time. Ideally, the same caregivers should facilitate this care at each visit to engender trust and to improve the continuity of thought, process and action.
- *Congruence in care*: Everyone in the Health Team should not only be giving the same information, but should also have the same insightful approach (based on a set of commonly shared and communicated values attitudes and beliefs) towards diabetes management. The person with diabetes will be reassured by the agreement and harmony they see and be more confident (a feeling of "self-efficacy") to practise what they have been taught.
- *Concordance* (or agreement within the Team, including the patient): A person with diabetes has to balance the demands of life, diabetes and diabetes management with the emotional, spiritual, structural, financial, and social resources available to them. Everybody must understand and accept the degree of tension that is being experienced and of the ability of the

person with diabetes to cope with it. This will help to ensure an open, trusting care process and achieve maximum adherence to therapy.

- *Communication*: Good communication is a prerequisite to concordance – patient and diabetes team must be open and truthful at all times and most importantly must *listen* to each other.
- *Conceptions* of diabetes: Previous experiences of diabetes treatment successes and failures result in a set of values, attitudes and beliefs, which guide future feelings and behaviours towards diabetes. We must assess these and factor them into any treatment plan.

Important Structural Principles of Integrated Diabetes Care

For the person with diabetes to self-manage their condition, they need the support of a diabetes team that provides care responsive to their needs from diagnosis to the management of chronic complications of diabetes. Diabetes UK lists the following five "key enablers of integration" [17]:

1. Integrated information technology systems
2. Aligned finances and responsibility
3. Care planning
4. Clinical engagement and leadership
5. Robust clinical governance

How Does the CDE DMP Approach Measure Up?

1. *Integrated Information Technology Systems*: All centres on the CDE Network are obliged to use a customized internet-based clinical management programme to enter all patient contacts, findings, diagnosed complications, key clinical outcomes, medications dispensed and laboratory results. Several of the private pathology laboratories in South Africa, serving up to half the DMP patients, are able to upload the relevant results directly into the CDE system, but centres that elect to use other certified laboratories need to enter their results manually. Patient confidentiality is assured by a multilevel, role-dependent password system. The Central Administrative Office has real-time access to all data. This facility is utilized to download, collate and check patient and Centre compliance with the "Minimum Care Guidelines" outcomes including HbA_{1c} trends and complication rates and to present this outcomes data to funding organizations. This ensures that all accredited providers providing care are able to access and add to a patient's data, obviating the need for file transfers. We can identify "at risk" and defaulting patients using data thresholds and follow them up.
2. *Aligned finances and responsibility*: The unique structure of the CDE doctor network allows for appropriate patient referrals to specialists as required and a patient specific specialist clinical advisory service. The CDE specialists make themselves available for telephonic/E-mail advice and face-to-face referral consultations, at no charge, for patients registered on the CDE Managed Care Programme. Because of this, complicated patients, and their attending doctors, have easy access to higher levels of expertise within the same network.

In addition, the new CDE Managed Care Programme Model makes provision for an annual clinical review of every single patient, by a CDE specialist. For this review, the CDE specialist accesses the electronic health record of patient, and provides clinical and therapeutic advice, to the CDE treating doctor. This approach ensures optimization of every patient's therapy and care strategy in a highly cost-effective manner.

3. *Care planning*: Diabetes UK (2014) [17] defines care planning as a "continuous process, in which clinicians and patients work together to agree goals, identify support needs, develop and implement action plans and monitor progress. People with diabetes should have active involvement in the care planning process of deciding, agreeing and owning how their diabetes will be managed."

Many of the problems surrounding the provision of adequate person-centred care for those with diabetes revolve around the pressures of clinical practice and a lack of time. Good diabetes management requires attention to a number of clinical parameters:

1. (Near) normalization of blood glucose
2. Control of co-morbidities and risk factors
3. Attainment of normal growth and development
4. Prevention of acute complications
5. Screening for chronic complications

To fit all this *and* a holistic, patient-centred collaborative approach into a busy general practice, the servicing doctor and other team members must understand that diabetes cannot be "dealt with" coincidently during a patient consultation for an acute condition. It requires a specific individual consultation of at least half-an-hour. This can be achieved by the doctor setting aside a specific time for a "diabetes clinic," be it a morning a week, a day a week, or a day a month, depending on the number of patients with diabetes being serviced. Each patient should have a pre-booked half-hour appointment. Patients should regard this as the equivalent of taking themselves in for a "routine service" every 6 months. In a resource-poor environment, one can make use of group education sessions. A registered nurse (ideally a diabetes nurse educator) performs the vital roles of team coordinator and patient advocate, mentor, counsellor, coach and self-management facilitator. In more "stretched" settings, the DNE can also assist with measuring blood pressure, weight and abdominal circumference of the patients, ordering the relevant laboratory investigations, and providing basic foot screening. The DNE can also download and check home blood glucose monitoring records. With the average number of patients at any one CDE Centre seldom exceeding 200, CDE healthcare providers have the time to provide individualized care to patients and the patients feel recognized as individuals.

Centre for Diabetes and Endocrinology patients are also encouraged to regard their diabetes centre as a place where they are welcome and can present for advice or discussion with their nurse educator at short notice. Patients are always asked to present their "agenda" at every consultation so that their perspective is always respected and recognized. This practical application of the "Medical Home" concept [41–43] and the central role of the patient in the diabetes team have been an integral part of the CDE philosophy since our inception.

4. *Clinical engagement and leadership*: We founded the CDE on a robust background of healthcare provider training and clinical and academic support, which has developed continuously over the past two decades. Our Central Office Team in Johannesburg is passionate about teaching diabetes care to anyone interested and we are active in exchanging diabetes knowledge with colleagues across the world. The following mechanisms are in place to attract and retain the best-skilled and most passionate people in diabetes to our Network:
    - General practitioners who are not accredited endocrinologists, and all DNEs who wish to join the CDE Network, are obliged to attend a comprehensive and person-centred "5-Day Advanced Course in Diabetes Care for Health Professionals." We present this course, covering all aspects of practical diabetes management, several times yearly. All practitioners interested in diabetes are welcome to attend. During the 5 days of the course, the faculty has opportunity to identify those attendees who show exceptional passion for and insight into diabetes. These practitioners are encouraged to take their skill and interest further, as part of the CDE network or not. Many of these practitioners choose to approach the CDE to accredit as a CDE provider. This may be one of the reasons why practitioners in our Network are of a high standard. In the past two decades, we have trained over 6000 healthcare professionals from all over the world in the principles of best-practice diabetes care.
    - As an annual follow-up to the CDE 5-day course, the CDE also hosts an annual national "Postgraduate Forum in Diabetes Management" which all members of the CDE Network are obliged to attend. All other interested healthcare professionals are also welcome to attend. This weekend event, in its 18th iteration for 2016, has a busy academic programme consisting of lectures, discussion groups and workshops on current and new concepts and modalities in diabetes management. A "CDE faculty" of senior endocrinologists in the CDE Network presents and facilitates the Programme. No honorariums are offered or paid for this service and companies involved in the provision of diabetes-related pharmaceuticals and diagnostics (although welcome to participate in a concurrent trade exhibition and offer company-branded pre-forum satellite events) have no say or part in the development, content and presentation of any aspect of the forum academic programme. This assures participants that the programme will provide an objective and unbiased review of the latest in diabetes care.
    - For any healthcare professional nationwide who has demonstrated a keen interest in furthering his or her diabetes knowledge and skill we facilitate subsidized (sponsorship is sought by CDE Central Office for a portion of the fees) attendance of Masters level Postgraduate University Diplomas in Diabetes Care (University of Cardiff Diabetes Diploma/University of South Wales Diabetes Diploma). Both are online distance learning courses with annual face-to-face introductory lectures at the CDE Central Office in Johannesburg and can be extended for an extra year to earn an MSc in Diabetes. This initiative has provided a major boost to diabetes care competence in South Africa. The local regulatory environment has effectively halted the development of local diabetes courses (even though the expertise exists in South Africa), so the CDE sought out International

methods of up skilling our local healthcare providers. A number of CDE faculty members have "Recognized Teaching Status" with these universities and are tutors on the courses.

- In addition, all members of the CDE Network receive complimentary copies of our quarterly in-house extract of current diabetes literature, produced by one of the senior endocrinologists in the Network, as well as our "official journal for diabetes healthcare professionals," the *South African Journal of Diabetes.*
- Recently, the CDE has established an online forum, which allows any CDE Centre, or team member to post questions and cases for comment and advice from the CDE faculty.

The main motivation for improving outcomes amongst the CDE centres appears to be a combination of concern to demonstrate good care and outcomes with the need to avoid hospital admission at the doctors' own expense. Overall, however, most of the centres enjoy the opportunity to become involved in long-term chronic disease management and in being part of a successful nationwide network regarded as Centres of Excellence by the medical funders. A key aspect of the CDE Programme is that the treating doctor and not the funder, is the "gate-keeper" and is wholly responsible for all related costs. This includes employing or paying for the services of a DNE, podiatrist and dietician. The clinical diabetes care given by the DMP is closely aligned to the International Diabetes Federation definition of a "standard" level of care [44]. Although the DMP concentrates on diabetes (glycaemic) control, other risk factors such as dyslipidaemia and hypertension are aggressively monitored and treated. Each patient is seen by the same named team of allied healthcare professionals and the same doctor. A key aspect of the CDE Network is that, while outcomes and standard of care are monitored, each trained doctor and Centre is free to treat their patients in any way they prefer, with their choice of any medication or insulin, as long as adequate outcomes and patient safety are assured. Generally, insulin therapy is started early and aggressively to attain and sustain glycaemic targets.

With these interventions, our accredited practitioners are generally highly empowered, motivated, insightful and knowledgeable individuals who really understand the demands of integrated, patient-centred care.

While Diabetes UK views engaging people with diabetes in a direct role in planning education and training needs as vital in this key enabler of integration, people with diabetes in South Africa are extraordinarily apathetic in getting involved in diabetes care at a political, governance or advocacy level. As a result, we have not made any progress here.

5. *Robust clinical governance*: Diabetes UK (2014) [17] defines clinical governance as "a system through which…organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish."

The overriding philosophy of the DMP is to provide total patient care for persons with diabetes utilizing a trained team of healthcare professionals, including doctors specifically trained in diabetes management and encompassing a significant component of financial risk sharing.

We assure compliance across the CDE Network to our Minimum Care Guidelines and the principles of "Good Clinical Practice" in two ways. In addition to the internet-based clinical management programme previously discussed, the CDE employs a full-time medical practitioner who conducts ongoing peer review and audit of the participating centres on the CDE Network. This both by monitoring the data entered onto the online database and by visiting the centres regularly and unannounced to inspect patients' written records, laboratory results and reports from outside healthcare providers. Our auditor visits each Centre on at least an annual basis. Any Centre team found to be underperforming by not fulfilling the CDE Minimum Care Guidelines or not following principles of Good Clinical Practice is counselled, coached on improvements required and then placed on probation for 3 months. On re-audit, if the Centre has not rectified the deficiencies, it is closed. Regular peer review and monitoring are part of our ethos. This has been an accreditation criterion for our Network since its inception.

No incentives are offered to CDE centres for improvements in HbA_{1c}, as this is an expected outcome.

We have relatively few difficulties in implementing our Programme requirements with our providers. We achieve this by having committed buy-in from all stakeholders before a CDE Centre is allowed to operate. This contention may be supported by a study by Pringle *et al.* [45], who attempted to assess variables of process of care to determine their relative effects. They report that patients who attended a practitioner with an interest in diabetes and those that saw a dietician had a marked positive effect on HbA_{1c} values. This corresponds well to the principles inherent in the CDE DMP.

Since each team is responsible for not only the costs of hospital admission for acute diabetes-related emergencies, but also ensuring good clinical outcomes, there is little resistance from centres for providing the best possible medication, even if it is more costly, to achieve these outcomes in a particular patient.

The CDE does not practise in a vacuum and is subject to oversight by the Council for Medical Schemes (CMS), a statutory body established by the Medical Schemes Act (131 of 1998) to provide regulatory supervision of private health financing through medical schemes. Council governance is vested in a board appointed by the Minister of Health, consisting of a Non-executive Chairman, Deputy Chairman and 13 members. The Executive Head of the Council is the Registrar, also appointed by the Minister in terms of the Medical Schemes Act. The Council determines overall policy, but day-to-day decisions and management of staff are the responsibility of the registrar and the executive managers.

The CDE is registered as an accredited managed care organization with the CMS. Every 3 years we have to submit to an intensive assessment of the extent to which we meet the conditions set out for accreditation by the Medical Schemes Act, including if we are fit and proper, if we have the necessary infrastructure and are financially sound. This ensures that entities contracting with medical schemes have been duly accredited as required by the Act. It has been of interest to the CDE that the CMS have modelled their accreditation and audit criteria for managed care organizations on the extensive clinical, administrative, healthcare provider

training and mentoring and network commissioning, coordination and auditing competencies that exist in the CDE Network and our Diabetes Management Programme.

Part VIII: Conclusion

The CDE trains, administers and audits the biggest network of diabetes providers in Africa, providing care excellence to many people with diabetes. Our capitation-based, fully integrated care model has excellent clinical and cost-efficacy outcomes, achieved largely by a geographically and economically diversified network, run primarily by primary care physicians, with the backing and support of a small group of certified endocrinologists. This demonstrates that improved glycaemic control and better outcomes are achievable in a wider primary care setting. Primary care practitioners *can* be trained in the core principles of diabetes management and attain satisfactory outcomes. However, to achieve this, adequate training, a holistic team approach, ongoing oversight and review and adequate financial reward are required to ensure service sustainability. Furthermore, it is apparent that Managed Care Programmes for diabetes which pass on the risk and "gate keeping" to the doctor and which focus on outcomes rather than cost-containment, are successful and cost-effective in both the shorter and longer terms. Fears that capitation-based programmes may result in under servicing are unfounded, provided the servicing doctors understand the principles of chronic disease management and are judged on outcomes and take risk for failure to attain these.

We have achieved International recognition for our work and our model of care. We are working hard to set up networks of providers and funders to ensure our continued existence and, if possible, to help make financial, clinical and moral sense to any future NHI model. We work on low profit margins, enough to sustain and grow us as a business, but not to "milk" the healthcare system of vital funds.

We have also provided diabetes education to thousands of healthcare providers through the medium of evidence-based, IDF aligned diabetes training courses since our inception. This has helped to fill a huge void in diabetes competence left open by local universities and healthcare policies. The training of healthcare providers is also essential to the success of diabetes care in the public health sector – in this vein we have already provided free training via attendance at our 5-day courses for nearly 50 public health employed health professionals. In addition to our local courses and national meetings, we are currently enabling healthcare providers to obtain Masters level diabetes qualifications at very little cost to themselves. We have changed diabetes care in South Africa and beyond.

Although we have record of more than two decades of successful community practice and steady expansion in a financially and politically hostile environment, based on sustainable business principles (no grants or Government assistance) and person-centred, ethical care, much more remains to be done. As a self-aware organization, we know that we only care for a very small part of the South African population with diabetes; multitudes do not receive adequate care and support. This we believe is a tragedy. Many of the contracted medical schemes have made membership of the CDE DMP voluntary, resulting in a negative selection bias; those with newly

diagnosed type 2 diabetes who perceive themselves to be "well" and whose primary care doctors consider them to be "controlled" often elect not to join. This has limited the potential growth and influence of this model in providing better care to more South Africans that make use of private healthcare.

A recent report by the International Finance Corporation [46] noted that, while the role of the private sector in African healthcare continues to be "contentious," better collaboration between both the public and private sectors would be the most efficient way of extending high-quality healthcare across the continent and crucial to improving healthcare provision in Africa. A recent academic study by Volminck *et al.* [47] looked at a cost-effectiveness analysis and potential utility of applying the private sector CDE DMP capitation model to the management of type 2 diabetes in the South African public sector versus "usual practice." Probabilistic modelling showed all iterations of the CDE DMP to fall below the accepted "Willingness-to-Pay" (WTP) threshold (i.e., it was cost-effective) and that it could contribute to increased life expectancy in South Africa. The study recommended that a pilot study of the CDE DMP be done to explore the practical translation of this analysis. Currently, however, the CDE lacks the political recognition and acceptance to enable a public-private partnership (PPP) with the South African Department of Health. We trust that this status quo will change and open an exploration of the possibility of better diabetes care to our population at large.

Abbreviations

ACE-I	Angiotensin-converting-enzyme inhibitors
ADA	American Diabetes Association
ARB	Angiotensin receptor blockers
CDE	Centre for Diabetes and Endocrinology
CMS	Council for Medical Schemes
DCCT	Diabetes Control and Complications Trial
DNE	Diabetes Nurse Educator
DMP	Diabetes Management Programme
DKA	Diabetic ketoacidosis
HONK	Hyperosmolar non-ketotic coma
HQA	Health Quality Assessment
NHANES	National Health and Nutrition Examination Survey
IDF	International Diabetes Federation
NHI	National Health Insurance
PMB	Prescribed Minimum Benefits
PPP	Public-Private Partnerships
UKPDS	United Kingdom Prospective Diabetes Study
VISS	Vascular Diabetic Complications in Southeast Sweden
WESDR	Wisconsin Epidemiologic Study of Diabetic Retinopathy

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