Insulin like Growth Factor and its Therapeutic Potential for DM Complications: Mechanism and Metabolic Links: A Review Article

Belete Biadgo¹, Workineh Tamir², Sintayehu Ambachew²

¹Department of clinical chemistry, School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar, Ethiopia. ²Department of Medical Laboratory Science, College of Medicine and Health Sciences, Debre Markos University, Debre Markos, Ethiopia.

Address correspondence to: Belete Biadgo, e-mail: beletebiadigo@yahoo.com

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Abstract

The insulin-like growth factor (IGF) system, is an important system in normal physiological functioning of the body. In Diabetes mellitus (DM), the IGF / Insulin like Growth Factor Binding Proteins (IGFBPs) levels alteration have been described mainly in vascular complications. Therefore, this review was aimed to explore the role of IGF system in reducing DM complications and its role as potential therapeutic target.

IGF-I have a role for growth and developmental process of neurons. Low concentrations of IGF-I have been associated with neuropathy and other DM complications. Moreover, Impaired IGF synthesis and function resulted in cellular senescence and impaired vascular endothelial proliferation, adhesion, and integration. Of note, high IGF-I bioavailability may reduce the inception of diabetes associated complications in DM patients. The mechanism for normal functioning of IGF-I is implicated by increasing nitric oxide synthesis and potassium ion channel opening in cardiovascular physiology, which improve the impaired small blood vessel function and reduce the chance of occurrence of diabetes complications associated with reduced concentrations of IGF-I. In conclusion, IGF may become as an alternative therapy for DM and DM associated complications. Therefore, future studies should emphasis on the mechanism of actions and therapeutic potential of IGFs in reducing the risk of developing and the progression of the disease in different clinical settings.

Keywords: IGFs · IGFBPs · DM complications · insulin resistance

1. Introduction

The Insulin Like Growth Factor (IGF) system involved in the regulations of mammalian cell growth and differentiations, proliferation and survival [1]. The system affects every organ system in our body. IGF-I itself is a small protein comprising of 70 amino acids, with a molecular weight of 7.65kilo Dalton, and the gene is located at chromosome 12q23 [1]. It is mainly produced by the liver cells although it is produced by many cells in our body [2].

The IGF system comprises of two cell-surface receptors (IGF-I and IGF-II) receptors, two ligands, IGF-I and (IGF-II) and comprises, about 6 high-affinity IGF-binding proteins (IGFBP1 to IGFBP6) [3,4], as well as associated IGFBP degrading protease enzymes. The entire system is strongly controlled by a feedback loop involving Growth Hormone (GH) secreted by the pituitary, and GH production and secretion controlled by Growth Hormone Releasing Hormone (GHRH) at the hypothalamus [4,5] (Figure 1).

IGF-I and IGFBP-3 are GH dependent [6], while IGFBP-1 is insulin regulated and IGFBP-1 production from the liver is significantly elevated during insulinopenia while serum levels of bioactive IGF-I is increased by insulin [7]. The production of IGFBP-3, 4 and 5 is stimulated by GH. IGFBP-3 is formed by the liver sinusoidal cells, at the junction of the intravascular space. In the circulation, IGF-I is mainly bound to IGFBP-3 and this binary complex then binds to a large protein called the acidsubunit (ALS) to form a ternary complex [8,9].
Insulin and IGF-I are two related peptides with similar structure. They facilitate their effects by interacting with their corresponding receptors such as the insulin receptor, and IGF-I receptor. The receptor ligand interactions induce intracellular signaling cascades resulting in metabolic or mitogenic effects [10,11] and involved in regulation of metabolism but its over production in some pancreatic and non-pancreatic cancers has been linked to severe hypoglycemia [11].

Insulin encourages the constitutive secretion of IGF-I from the liver. In turn, IGF-I overwhelms insulin secretion even in normoglycemic situations [12]. Furthermore, previous study showed that, IGF-I upsurges insulin activity and peripheral glucose utilizations, decreases hepatic glucose production and improve the lipid profile in diabetes mellitus (DM) patients [13].

The IGFBP-1 is regulated mainly by insulin. It interacts with IGF-I and IGF-II, and used as a shuttle of IGFs to target tissues and regulates the action of free IGF-I. The IGFBP-1 is regarded as the primary important regulator of IGF-I bioactivity and has an important part in the progression of DM and DM related complications [14]. Lewitt, et al; reported that the IGF system has an imperative patho-physiological role across the range of metabolic abnormalities including obesity, insulin resistance (IR) and DM [15]. The exact mechanisms by which type 1 diabetes (T1DM) and poor glycemic control to the GH-axis, and its interaction with IGF-I and IGFBP-3 remain to be determined. Nambam and Schatz have shown that GH insensitivity with low concentrations of IGF-I is often perceived in T1DM patients [16]. However, controversies have been described in DM complications such as diabetic retinopathy (DR) [17]. According to Bazzaz, et al growth factors are associated with the development of DR, diabetic nephropathy (DN) and diabetic neuropathy (DNP). However, this article showed that growth factors including vascular endothelial growth factor (VEGF), IGF-I and tumor necrosis growth factor revealed a protective role on the progression and development of DM complications [18].

The pathogenesis of DR is a complex process involving ischemia/hyperglycemia and growth factor can result in neovascularization and vision loss. There is controversy in serum IGF-I levels correlation with the progression of retinal neovascularization in clinical diabetes and increased or decreased concentrations of IGF-I in the vitreous or serum of patients with DR [19]. Neamtu, et al have revealed that decreased concentrations of IGF-I was positively correlated with DM and DM related complications [20]. Evidence has suggested that patients with T1DM can exhibit aberrations of the GH/IGF/IGFBP axis like GH hyper-secretion, decreased in concentrations of circulating IGF-I and IGFBP-3, and elevated levels of IGFBP-1 [12]. These abnormalities are not only exacerbating hyperglycemia in patients with T1DM but also share its role on the pathogenesis of DM related complications [21]. In addition, IGF-I deficit also has been reported to have significant association with risk of developing impaired glucose tolerance, IR and Type 2 Diabetes Mellitus (T2DM), the study also hypothesized to be intricate in the pathogenesis of schizophrenia [22]. Furthermore, Knott in 1998 has also presented a
clear association between high levels of IGF-I and the progression of DR [23]. Therefore, the aim of this review was to narrate a large body of evidence on the therapeutic potential of human IGF-I for DM complications and to understand the mechanism and metabolic links of IGF in DM complications.

2. The physiology of IGF system

The IGF system is encompassed of IGFs, IGF-I and IGF-II receptors, binding proteins and IGFBP specific proteases [9]. Roith, et al., [24] stated that, IGF decreases the chance of developing DM, cancer and malnutrition [24,25]. The IGF regulatory system in each organ is tissue specific including liver and kidney, heart and other tissues but all share similar components [26-28].

The IGF-I and IGFBP-1 are regulated by pituitary GH and IGFBP-3. IGF-I and IGFBP-3 form complexes binding with ALS and prevents the premature degradation of IGF-I by circulating IGF-I proteases. Its extravagation into the extracellular space, extending the half-life and transport in to specific target tissues [16]. Aguirre, et al reported that, IGF-II has similar physiological properties with IGF-I and the actions have remained poorly characterized but the appropriate roles for fetal growth and development, and cerebral protection has been documented [29].

2.1 Physiology of insulin and IGFs

Insulin is secreted from the β-cells in the pancreas. It has both endocrine and exocrine function. Insulin consists of two peptide chains “A” and “B”. The other “C”-peptide is formed and cleaved off when pro-insulin becomes active insulin. Insulin increases glucose uptake in muscle and fat by stimulating the translocation of glucose transporter 4 from the cytoplasm to the cell surface but inhibits glucose production in the liver. It also stimulates lipogenesis, glycogen, protein synthesis, cell growth and differentiation. The functional defect and/or deficiency of insulin causes DM with elevated fasting and postprandial glucose levels and elevated free fatty acid levels [10].

The GH-IGF axis includes the hypothalamic pituitary axis for production of GH and its receptor for IGF production, IGFBP for transport of IGF and IGF receptor for IGF action [30]. Laron, et al., [31] stated that IGF-I acts as an endocrine hormone secreted by the hepatocytes and transported to other tissues and secreted also by other tissues including cartilaginous cells; acts locally as a paracrine hormone and it can act in an autocrine manner in oncogene [31]. Therefore, IGF are and insulin are proteins with high amino acid sequence similarity. They have structural similarity but control different aspects of growth, development and metabolism. IGF-I and insulin fully activate IGF-I and Insulin receptor, but they can also interact and activate the other receptor with low affinity [17,26,32,33].

2.2 Insulin like growth factor-I and insulin like growth factor-II

The IGF-I is peptide hormone consisting of 70 amino acids with “A “and “B” chain connected by disulphide bonds and “C” peptide region [31,34]. The IGF-I gene is under GH control in certain tissues such as liver but is also responsive to factors like developmental signals, nutritional status, DM, aging and neural activity. IGF-II gene is also responsive to all above conditions with exception of GH. The IGF-II bind to the IGF-I receptor; it is believed that most actions of IGFs are through its receptor [26,30,32]. Bachner-Melman has showed the functions of growth factors and stated that both have role in mediation of GH action, stimulation of growth of cultured cells, stimulation of the action of insulin and involvement in both development and growth [35]. The IGF-I is necessary for normal insulin sensitivity and impairment of IGF-I synthesis that results in IR. IGFs in biological fluids are accompanying with IGFBPs which are the major regulators of IGFs’ biological activity and metabolic signaling pathways [26].

2.3 Interactions of insulin receptor and IGFs

Both insulin and IGF-I have their own receptors such as insulin receptor and IGF-I receptor from the same family of tyrosine kinase receptors [10]. Lewitt, et al stated that, the IGFs interact with insulin receptor A and B isoforms, IGF1 receptors and hybrid receptors (Insulin receptor A-IGF-I receptor and Insulin receptor B-IGF-I receptor). This is used to arbitrate signals in diversity of tissues to harmonize protein, carbohydrate and fat metabolism. Interestingly, liver cells and mature adipose tissues cells have ample Insulin receptor B and insulin has a 2 fold higher affinity for Insulin receptor B than IGF-I [15].

The IGF-I receptor has been found in various body systems including brain, testes, liver...
and bones. This suggests an important paracrine and endocrine role of IGF. Insulin binds to the IGF-I receptor with lower potency compared to IGFs, and the IGF binds to the insulin receptor to activate the reduction in blood glucose level in the body [36]. The IGF-II receptor almost exclusively binds with IGFBP-II; and play a minor role in the growth promoting effect of IGF [30,31].

Previous study has reported that nutrition and GH stimulate the synthesis of IGF-I in liver and other tissues. The study revealed that gender differences exists in the hepatic sensitivity to GH, and women require more GH to synthesis IGF-I in liver and other tissues [37]. The IGFs that reach to the pituitary hinder GH synthesis in a feedback loop and GH has an imperative metabolic roles that are independent of IGF-I effects, as well as stimulation of lipolysis and inhibitory effects on insulin signaling in fat and muscle [38]. Thus, IGF feedback inhibition of GH, by dropping the direct metabolic effects will upsurge insulin sensitivity. Dynkevich, et al had concluded that, IGFs directly control protein, carbohydrate and fat metabolism and IGF-I also augments insulin sensitivity, independent of its consequence on GH [39].

2.4 Insulin like growth factor binding proteins (IGFBPs)

The IGFBP family is a critical component of the IGF system, which controls the biological actions of the IGFs and may also be capable of IGF independent actions [33]. Back, et al., [10] have reported IGFBPs as regulators of growth factors bioavailability by forming IGFBP-IGF complexes [10]. According to Adamek, et al suggestion, IGFBPs are also used to supply IGFs in specific tissue sections and constrain activity of IGFs by depressing availability of their receptors and shield it from proteolytic degradation [26]. Moreover, soluble IGFBPs are specific proteins that are capable to form interactions with IGFs in extracellular and interstitial fluids of living organisms [40]. In the plasma, 99% of IGFs are interacted with family of compulsory proteins, which control the accessibility of free IGF-I (fIGF-I) to the tissues. In humans, nearly 80% of circulating IGF-I is transported by IGFBP-3, a ternary complex comprising of each with one molecules of (IGF-I, IGFBP-3 and ALS) [31,32].

The unbound IGFs and IGFs in binary interactions have short lifespans in the circulation and estimated within minutes to hours. Total IGF estimation in single blood specimen consequently undervalue this dynamic IGF turnover and fail to show the appropriate tissue IGF production, which contributes to the activity of IGF at the cellular level [33,41].

A study has reported that, the IGFBP-1 concentrations are repressed in relative to the upsurge in insulin levels in obesity and low concentrations forecast the development of T2DM. The Visceral adiposity and hepatic steatosis along with a long-lasting inflammation contribute to the IGF system phenotype in persons with metabolic abnormalities and T2DM. The IGF system is concerned in the vascular pathophysiology and other complications and is therefore, it may have a potential therapeutic target [15]. Importantly, the incidental effects of IGF-I that impact metabolism include clampdown of GH and insulin secretion. The activities of IGF-I are controlled by IGFBPs. In obesity and metabolic syndrome (MetS) there is foremost dysregulation of IGFBP secretion ensuing change in the levels of free IGF-I. In T1DM, IGF-I synthesis is evidently reduced while in T2DM various deviations arise in IGF-I actions such as sensitization to its mitogenic actions in some target tissues including liver, pancreas and peripheral tissues [42].

3. IGFs, IR and diabetic complications

3.1 IGFs and IR

IR can be defined as a state where target tissues show a reduction in responsiveness to insulin. Evidence reported that, in T1DM a reduction in insulin levels in the portal vein results in dysregulation of the GH/IGF/IGFBP axis [43]. T1DM has been associated with hepatic GH resistance and increased production of IGFBP-1 and 2. Decreased levels of IGFBP-3 resulting in reduced levels of circulating IGF-I [10,43]. The beta-cells of pancreas secrete insulin in response to an augmented blood glucose level during normal condition, to compensate for the insulin resistant state, cells increase basal and post-prandial secretions of insulin. However, cells can no longer compensate and fail to respond appropriately to the impairment in glucose disposal [44]. These lead to the disorders of glucose homeostasis and to the development of hyperglycemia. In turn, this leads to development of peripheral IR and impaired insulin action [44,45].

IR is also a pathological condition results de-
crease in efficiency of insulin signaling for blood sugar regulation [44]. It is a key component of MetS. It also increases the risk of various diseases including T2DM, cerebrovascular, coronary artery diseases and neurodegenerative disorders [46].

Genetic disorders of IR are characterized either by mutations affecting the insulin receptor or defects in post-receptor sites. For example, T2DM is associated with down regulation of peripheral insulin binding sites and upregulation of tissue specific IGF binding [21]. Furthermore, evidence suggests that IR is in classic insulin target organs along with the associated hyperglycemia and these are the pathological hallmark of metabolic disorders such as obesity and T2DM [46].

A study has investigated the effect of IGF-I on insulin sensitivity and its relation to T2DM. National Health and Nutrition Examination Survey III reported a higher risk of IR, MetS and T2DM in study participants with low serum IGF-I level [21].

A mice model had shown that a deletion of hepatic IGF-I production has led to 80% reduction in IGF-I concentrations that increased concentrations of insulin in blood and resulted in disorders in blood glucose concentration and abnormal glucose clearance [47,48]. Furthermore, supporting evidence by Friedrich, et al reported a negative relationship between IGF-I levels and IR measured by the homeostasis model assessment of IR [49].

Evidence suggests that the IGF axis may play a role in glucose homeostasis. Rajpathak, et al revealed that exogenous administration of IGF-I decreases serum glucose concentrations and improves insulin sensitivity in individuals with and without T2DM [34]. In addition, Insulin and IGF-I are capable of thought-provoking glucose uptake, glycogen synthesis and the decreasing of protein catabolism [42]. IGF-I has little effect on the adipocyte and mature liver due to lack of IGF-I receptors on these sites but recombinant human IGF-I has been shown to overwhelm hepatic glucose production via unknown mechanisms and recombinant human IGF-I therapy in patients with severe IR might be efficacious [50].

Deviations in GH and IGF-I function alter insulin's ability to maintain normal carbohydrate homeostasis [42]. In mice model, IGF-I synthesis in the liver is eliminated and then crossed with mice that over express a mutant form of GH that prevents GH activation of its receptor showed that GH is a major determinant of IR in IGF-I deficient mice [51].

Administration of IGF-I to normal human showed, lower concentrations of glucose that is nearly 1/10th as potent as that induced by insulin. Supporting evidence by Clemmons, et al, revealed patients with extreme IR IR showed improved insulin sensitivity and carbohydrate homeostasis after IGF-I administration [51].

In summary, of hepatic IGF-I production has a role in reduction of IGF-I concentrations that directed to increased concentrations of insulin in blood and resulted in disorders in blood glucose concentration and IR [47-49] (Figure 2).

Figure 2: Liver derived circulating IGF-I in muscle insulin sensitivity. Liver-specific IGF-I gene deletion is associated with a noticeable decrease in circulating total IGF-I levels and elevated GH levels. Subsequently, insulin insensitivity at the level of the muscle as well as islet cell hyperplasia are associated with hyperinsulinenia (adapted from [49]).

3.2 The metabolic link between IGFs and diabetes mellitus complications

Insulin regulates cellular energy supply, macronutrient balance and direct anabolic processes of the fed state. It is crucial for the intracellular transport of glucose into insulin dependent tissues including skeletal muscle, adipose tissue and liver [52]. Like insulin, IGF-I also promotes protein synthesis in skeletal muscle and several other tissues. On the other hand, insulin appears to have an incidental consequence on the metabolism in vascular smooth muscle as there are only receptors for IGF-I in these tissues [53].

In humans, a study showed that, insulin upregulates hepatic GH receptor expression and increases net cell surface receptor availability in the portal circulation. Although GH and insulin have metabol-
ically opposed hormones, insulin has been described to have a permissive role in facilitating the action of GH. In children with T1DM low concentrations of GH binding protein secondary to low levels of portal insulin has been reported, this has an indirect consequence on the decreased levels of IGF-I [16].

The decreased level of IGFBP-1 in T1DM is thought to be caused by the absolute insulin deficiency. A study in T2DM patients showed that a decreased IGFBP-1 concentrations were assumed to be due to hyperinsulinemia [11,14]. Insulin levels become low during fasting to enable mobilization of fatty acids, glycerol from adipose tissue and amino acids from muscle but higher in the fed state [52]. The extent of insulin sensitivity may be predisposed by the composition of the diet and chronic energy consumption endorses hyperinsulinemia. IR complete stimulation of insulin secretion, triglyceride synthesis and fat buildup with down regulation of insulin receptors [53]. Furthermore, prospective data had designated that a relatively low levels of IGF-II may rise the risk of weight gain in T2DM patients. These strong inverse associations are independent of other risk factors for weight gain and obesity [54].

The effects of fasting on in vascular smooth muscle metabolism appear to be like the effects of DM on vascular metabolism throughout the early stages. Consumption of high fat diets tend to be related with IR principally in relation to saturated fat and trans-fatty acids because these fatty acids are play a role in development of IR through effects on the composition of membrane lipids [55].

The GH acts on IGF-I secretion which has metabolic actions on its own and depends on weight status. A Study showed that, IGFI is dependent on body mass index (BMI) with a maximal level between a BMI of 30-35 Kg/m2. This relation is reflected in severe GH deficiency indicating that GH independent IGF-I secretion represents an imperative metabolic regulator [56].

Previous study on the infusion of recombinant human IGF-I in IR clearly support IGF-I serve a role in the regulation of cell mass, insulin secretion and the regulation of insulin sensitivity. The energy sensing character of a cohesive IGF-I/insulin system controls lipolysis, proteolysis and IR [56]. Moreover, administration of IGF-I to patients with IR showed that an improvement in glycaemic status. Clemmons, et al reported, IGF-I was associated with lowering blood glucose concentrations and increasing insulin sensitivity in DM patients. However, DM patients are also sensitive to stimulation of adverse effects in response to IGF-I. IGF-I co-ordinately associates GH and insulin actions as well as having direct effects on intermediary metabolism [42].

Another study has also reported that, the IGF-I has implications on lipid and glucose metabolism [57] and its exogenous administration augments insulin sensitivity in healthy adults as well as T2DM patients. Sesti, et al., [58] had shown that in about 500 patients IGF-1 concentrations were autonomously associated with insulin sensitivity accounting for 10.8 % of its variation. IGF-I plasma concentrations for MetS, each unit increase in log transformed IGF-I concentrations was associated with a 90.5 % decrease in the risk of MetS [58].

In summary, GH, IGF and insulin have important in normal physiological role of the body. GH and insulin are metabolically opposed hormones, insulin has been described to have a permissive role in facilitating the action of GH and a relatively low levels of IGF may increase the risk of weight gain in DM patients. Administration of IGF-I to patients with IR may have a role that can improve glycemic status and implications on lipid and glucose metabolism.

3.3 IGFs and its association with diabetes mellitus complications

IGF-I applies anti-inflammatory and pro-survival effects on the vasculature ensuing in decreased vascular oxidant stress, apoptosis and inflammatory signaling. A reduced in IGF-I activity has shown to endorse cerebro-microvascular dysfunction, quicken endothelial apoptosis and diminish the regenerative ability of endothelium [59].

Low IGF-I levels have shown to forecast glucose intolerance and T2DM. The hIGF-I concentrations are linked with occurrence of DM in women with insulin concentrations beyond the median but below the median IGFBP-I concentrations. However, poorly managed T2DM patients are associated with an upsurge in IGFBP-3 glycation, which rises affinity for IGF-I and additional sialylation that has the opposite effect to decline IGF-I affinity [15].

Evidence are now evolving that dysregulation of the IGF system is intricate in the development of diverse complications of DM. The IGFs, specifically IGF-II has sturdy anti-apoptotic role tangled in proliferation of endothelial cells and numerous cancer cells lines. It has been argued that regional concentrations of IGFs may be more substantial than systemic concentrations
in the pathogenesis of DM complications [11,17]. Clinical surveys have verified that truncated circulating levels of IGFBP-1 are linked with T2DM while high serum IGFBP-1 levels are related with T1DM. The serum IGFBP-1 concentrations are found to be augmented in T1DM patients with microalbuminuria [14].

The IGFBP-3 is regulated by GH whereas the IGFBP-1 is regulated by insulin which down regulates the production of IGFBP-1. The portal hypoinsulinization of T1DM leads to higher amounts of IGFBP-1 which decreases the accessible bioactive fIGF-I. These effects are the concomitant chronic inflammation accompanying T1DM. Higher levels of pro-inflammatory cytokines such as tumour necrosis alpha and interleukin-1β induce IGF-I resistance. A study has shown that, higher levels of Interluekin-8 in T1DM have been related with lower IGF-I levels in adolescents [16]. Supporting evidence by Hedman, et al. [16] in 2004 had also studied the GH/IGF-I axis in adults with long standing T1DM. They speculated tIGF-I and fIGF-I were higher, while IGFBP-1 was lower. They revealed that low IGF-I not only leads to poor growth in children but may also have a role in IR and poor metabolic and cardiovascular outcomes [16].

In general, systemic administration of recombinant human IGF-I reduce the levels of insulin and a glucose in DM patient with reduced response to insulin which indicates IGF-1 is capable of increasing insulin sensitivity [50] and has the potential to have broad effects on IR and hyperglycemia.

3.3.1 Insulin like growth factor and retinopathy

The DR is a complication of DM that affects the eyes, results primarily from harm to the blood vessels triggered by the hyperglycemia. The DR consequences in the gradual loss of sight leading potentially to blindness. Nearly all people with T1DM and more than half with T2DM develop complications involving the retina [17].

Hyperglycemia primes to numerous biochemical aberrations that eventually lead to retinal ischaemia and vulnerability to dysregulated angiogenesis. Growth factors are up-regulated along with their individual receptor and disparity between pro-angiogenic and anti-angiogenic factors primes to new blood vessel formation in the retina. Due to the friable nature of the newly formed blood vessels and insufficient cell-cell junctions, the vessels are predisposed to outflow and hemorrhage, finally a consequences for retinal detachment [17,32].

The alterations of growth factors are believed to be significant in both initial and late phases of DR. The loss of pericyte and endothelial cell injury are two factors that may added exacerbate growth factors mediated proliferative response. These marks increased endothelial cell matrix deposition and basement membrane thickening, leading to proliferation and migration of endothelial cells and consequent neovascularization [17]. Moreover, failure of the Blood Retinal Barrier (BRB) is a bulbus feature of DR, venous occlusive diseases and cystoid macular edema. Intra-vitreal administration of IGFBP-3 conserves junctional truthfulness in the occurrence of VEGF or laser injury by reducing BRB permeability in part by modulating sphingomyelinase levels [60].

Previous study has verified that, circulating concentrations of t/fIGF-I are low in patients with T1DM compared with age and sex matched controls. Age-adjusted fIGF-I levels were expressively higher among those DM with DR than in DM without DR [21], but other study has indicated no real connotation between IGF-I levels and the progression of retinal disease [23].

The risk factors believed to be related with DR include course of DM, glycated hemoglobin, high blood pressure, low density lipoprotein cholesterol (LDL-C), and urinary micro albumin. The clear pathogenesis of DR was not speculated by authors but according to the report, GH and IGF-1 may also be involved in DR [61].

The role of IGF-1 in DR including other DM complications has been extensively studied. However, there are inconsistent rumors as to the relationship between IGF-I and the clinical stage of DR. It might be distinguished that; autocrine and paracrine tissue production of IGF-I might contribute to the variation in correlation studies [17].

The development of adjuvant treatments to enhancement diet, exercise, oral hypoglycemic agents, and insulin is immediately desirable and considerable to improve the quality of patient life. The neurobiology of IGFs has been premeditated in animals and a loss of IGF activity produces neurological syndromes that mimics the disorders of DR [32]. Moreover, insulin is the furthermore efficacious hormone for the treatment of hyperglycemia by mediating direct and indirect actions to lower hyperglycemia. The application of IGF-1 could be considered when an extreme IR existed or insensitivity whereby recombinit human IGF-I might be an alternative
strategy to normalize the blood glucose level and prevent the acute complications of diabetes [62].

In summary, the GH-IGF-I axis in the development and progression of DR has been inferred for decades when surgical removal of pituitary (hy-ppophysectomy) was first introduced as a treatment for DR. Rapid improvements in glycemic control can promote clinical regression of proteinuria and symptomatic neuropathy. These changes can also be attended by a momentous deteriorating of retinal disease, because progresses in glycemic control are conveyed by an increase in serum IGF-I levels and IGF-I has been also shown to act as an angiogenic agent in animal cornea and retina [21].

3.3.2 Insulin like growth factors and cardiovascular disease

Cellular senescence and impaired vascular endothelial proliferation, adhesion and incorporation play a critical role in the occurrence of macro-vascular disease [63]. Higher IGF-I bioavailability may protect the onset of ischemic heart disease, glucose intolerance in T2DM patients. This may offer improved metabolic control and prevent vascular complications. Other likely beneficial actions of IGF-1 in cardiovascular physiology include augmented nitric oxide synthesis and potassium channel opening [64]. This may clarify the weakened small vessel function related with low IGF-1 levels in patients with CVD through LDL cholesterol activated cytotoxicity and vascular smooth muscle cell apoptosis. The IGF-I possibly will also protect against plaque instability and rupture [49]. In patients with acute myocardial infarction, noticeably reduced IGF-I levels are linked with a poor outcome. The authors reported that intra-myocardial or vascular gene delivery of growth factors can progress symptoms and exercise capacity in patients with coronary or peripheral vascular disease [65].

Importantly, low IGF-I concentrations are associated with late mortality in patients with myocardial infarction, cardiac failure and DM. Interventions studies suggest that IGF-1 has anti-atherogenic actions owing to its multifactorial effect on CVD and related risk factors. The anti-platelet and anti-thrombotic effects of IGF-I exhibited a crucial effects in avoiding both vascular damage and unstable coronary plaques [66].

The short-term anti-inflammatory properties of IGF-I seem to decrease infarct size and progress left ventricular remodeling after myocardial infarction. Furthermore, IGF-I has also an immune modulatory activity which can inhibit the autoreactivity. This puts IGF-I as an important protein explaining the anti-thrombotic and anti-remodeling activities [68].

IGF-I increases the contractility of cardiomyocytes mainly by increasing intracellular calcium level and calcium sensitization of the myofilaments and conserves capillary density. The GH and IGF-1 are likely to increase protein synthesis in the cardiomyocytes. The re-uptake of calcium is also promoted by IGF-1 through the regulation of the sarcoplasmic reticulum Ca2+-ATPase (SERCA2) which is involved in diastolic function [67].

The IGF-I system especially low IGF-1, IGFBP-1 and high IGFBP-3 relate to increased CVD risk. The production of IGFBP-1 in the liver is down regulated by insulin. There is a correlation between low levels of IGFBP-1 and hyperinsulinemia which also can be linked with increased CVD risk. However, IGFBP-1 levels rise during the development of T2DM, regardless of persistent hyperinsulinemia, indicating increased hepatic IR during CVD progression [68].

In randomized trial for dilated cardiomyopathy, GH had neutral effects in heart function and symptoms. However, the concentration of IGF-I induced by GH rather than GH itself affects the improvement in heart function. IGF-I has proliferating, inotropic, vasodilator, and anti-apoptotic effects in cardiovascular system. Acute injection of IGF-1 into apparently healthy individuals and cardiac failure patients resulted in inotropic effects [69]. Furthermore, a study assessed the relationship between congenital heart disease and underweight in infants. The authors reported underweight infants with congenital heart disease had a significantly reduced energy intake and substantially low serum IGF-I and IGFBP-3 levels. The finding suggested that low levels of IGF-1 and IGFBP-3 were observed in nutritional deficiency. The authors recommend consecutive measurements of serum IGF-1 and IGFBP-3 may be supportive in monitoring the effect of nutritional supplement in congenital heart disease [70].

Therefore, IGF-I level has substantial associations with CVD, lower concentrations are associated mycardial infarction, cardiac failure. Measurement of IGF level in patients with CVD may improve the prognosis and predict outcome of the disease. Administration of IGF-I may lead to an increase in the production of nitric oxide which primes to the reduction of the systemic vascular resistance.
### 3.3.3 Insulin like growth factors and neuropathy

The DNP is a disorder sub-clinically or clinically evident in both peripheral and autonomic nervous systems [71]. Neuropathies are the furthestmost shared complication of DM affecting up to 50% of patients with DM in T1DM. Distal polyneuropathy becomes symptomatic after several years of diagnosis in T1DM but in T2DM patients neuropathy is detected at the time of diagnosis [72].

It is generally thought that diabetic neural instabilities may be a secondary significance of hyperglycemia, but this remains a debatable issue. IGFs are neurotrophic factors talent- ed in supporting neurite outgrowth and endurance in peripheral and central neurons [73].

Insulin, IGF-I and IGF-II are proposed to provide neurotrophic support for neurons but IGF activity is reduced in diabetes [74]. Neuropathy can be prevented by administration of IGF and both central and peripheral neurological disturbances share a common etiology involving IGF and treatable irrespective of hyperglycemia [32].

The mechanisms by which DM causes Central nervous system complications are not clear. In Central nervous system, apoptotic neuronal cell death has been designated in ischemic brain injury and in neurodegenerative diseases [75] including (Alzheimer disease, etc.). Furthermore, a study on a duration dependent neuronal apoptosis in hippocampus of T1DM rats has accompanied with neuronal loss and cognitive impairments [28].

In the peripheral nervous system of T1DM patients IGF-I, insulin, and C-peptide contribute to the development of axonal degenerative changes and participate in weakened regenerative capacities [75]. Nonetheless, IGF aberrations are less noticeable in T2DM which may in part account for the milder neurological complications in T2DM patients. Therefore, renewal of several members of the IGF system offers a realistic rational for prevention and treatment of DNP [28].

The IGFs have been shown to stimulate motor neuron proliferation and differentiation. It increases motor neuron myelination, inhibit demyelination, reduce neuron apoptosis during normal development and enhance axonal regeneration after injury. It also protects neurons from toxicity induced by chemicals, cytokines and cancer chemotherapy. T1DM is characterized both by a decreasing in tIGF-I levels and increasing sequestration of IGFs by higher levels of IGFBP-1 ensuing in a further decrease in bioavailable free IGFs [21]. In addition, in mice model, T2DM with peripheral neuropathy have lower serum levels of IGF-I and red cell IGF-I receptor when compared with non-neuropathic with DM and controls who are non-diabetes [21].

Therefore, in DNP, numerous metabolic and vascular changes inter-connect to cause damage to nerve cells in a similar way to that perceived in DR with the primary underlying feature being hyperglycemia. The changes include increased oxidative stress, formation of advanced glycation end-products, increased activity of the polyol pathway, activation of pro-inflammatory mechanisms and ischemia. These pathways have direct and indirect adverse effects not only on neurons but also blood vessels that source the nerves particularly in DM patients [76].

### 3.3.4 Insulin like growth factor and nephropathy

The DN is a major cause of morbidity and mortality in patients with T1DM and T2DM, about one-third of this population suffering from this long-term complication of DM and DM has become the leading cause of End Stage Renal Disease (ESRD) worldwide [77].

DN is a clinical syndrome detected by albu- minuria and continuous decline in the glomerular filtration rate [78]. Patients with T1DM progress early to ESRD as compared to those with T2DM [79]. The early physiologic abnormality in DN is glomerular hyper-filtration related to in- tra-glomerular hypertension and this is comple- mented by the onset of micro-albuminuria [79].

The kidney is a source of significant synthesis and target for IGF-I action [80]. In vitro IGF-I has been shown to be mitogenic for renal cells, promote nephron hypertrophy and stimulate tubu- lar phosphate transport. Supporting evidence by Thralkill, et al has stated that, the systemic ad- ministration of IGF-I causes increased renal blood flow and glomerular filtration rate [21]. Therefore, the IGF system is an important constituent for normal functioning of the kidney and enhancing repair of injured kidney but dysregulation of the system has been reported in a variety of kidney diseases.

### 3.4 Clinical/therapeutic potential of IGFs for diabetes mellitus and its complications

Growth factors are generally implicated in the development of DR and DN. In DNP VEGF, IGF-I and necrosis growth factor have a protective role. This differential impact of growth factors is partly related to the discrete patho
physiological nature of different endpoints [18].

Injection of IGF-I to patients who develop IR leads in good glycemic control. The IGF-I has been shown to be linked with glucose lowering effect and increasing insulin sensitivity. However, DM patients are sensitive to stimulation of side effects in response to IGF-I and the effect has greatly limited its practicality as a hypoglycemic agent [42].

The IGF-I serum levels usually have not been found increased in DM patients. Instead, there is IGF-I reduction at the systemic level most overwhelmingly in patients with poor glycemic control. At the tissue level, there is decreased IGF-I availability due to reduced serum f/tIGF-I and increased IGFBP-1 (as an inhibitor of IGF-I). During DM monitoring and follow-up to improve glycemic level, the serum level of IGF-I usually increases. This phenomenon explains the pathophysiology of the “bush fire” which is brief exacerbation of proliferative DR following better glycemic control. Hence, the relationship of retinal ischemia with both local IGF-I production, and IGFBPs and angiogenesis has been recognized [18].

The availability of recombinant human IGF-I has a potential to use the peptide in the treatment of a variety of disease states. In scientific literature, T1DM has received a consideration due to the relative portal insulin deficiency. This disorder is thought to be accountable for the decreased circulating levels of IGF-I [81].

Improved glycemic control has been described in patients with T1DM and T2DM after IGF-I treatment. IGF-I administration reduce the GH hyper-secretion of adolescents and adults with T1DM. The reductions in GH secretion were associated with decreased insulin requirements without alteration in glycemic control, this indicates an upsurge in insulin sensitivity [81]. The authors have also explored the effects of IGF-I infusion on glucose and protein metabolism in healthy individuals. They demonstrated that large doses of intravenous IGF-I have effects comparable to insulin on glucose metabolism, but the effects on protein metabolism are different and are categorized by decreasing in circulating amino acid levels [81].

Oral monotherapies did not achieve the target of intensive therapy in T2DM patients. Combination of insulin oral agents and diet can partially reduce DM complications. Intensive therapy reduced glycated hemoglobin levels by approximately 1% which is below results achieved by conventional therapy ensuing in a 35% lessening the risk of developing complications [32]. The effects of short-term administration of recombinant human IGF-I on glycemic control and control of the GH-IGF-IGFBP axis in patients with T1DM has been reported [21]. The study established that a single subcutaneous injection of recombinant human IGF-I (40 mg/kg) given at 1,800 hours give rise to elevated levels of IGF-I, reduced overnight secretion of GH and declined insulin necessities in 9 pubertal adolescents with T1DM [21]. Moreover, in both insulin and IGF-I are proficient in provoking glucose uptake, glycogen synthesis and the inhibition of protein breakdown. IGF-I has small effect on the adipocyte and hepatocytes because of the lack of IGF-I receptors, but recombinant human IGF-I has shown to inhibit hepatic glucose production via unknown mechanisms [50]. Therefore, recombinant human IGF-I therapy in patients with IR might be efficacious.

4. Conclusion and recommendations

The IGF system is very important endogenous means recruited daily for cardiovascular, metabolic related health disorders, IR and DM complications. The role of IGF-I in the occurrence of IR and DM complications has been described. An inverse relationship between the circulating levels of IGF-I (IGF-ItoIGFBP-3 ratio) and MetS, DM and CVD has been reported. Hence, it could indicate that low circulating levels of IGF-I can lead to MetS and raise the risk for CVD and DM complications.

Cellular senescence reduced vascular endothelial proliferation and adhesion plays an essential role in the progression of macro-vascular disease. However, higher IGF-I availability may defend against the onset of CVD and glucose intolerance in DM patients. Moreover, IGF-I upsurges nitric oxide production and potassium ion channel opening in cardiovascular physiology, which progress the weakened small vessel function linked with low IGF-I concentrations in patients with cardiovascular syndrome.

Therefore, IGF system is involved in the vascular pathophysiology during the progression and protection role of vascular complications, and it has also implicated in metabolic abnormalities. This is therefore, IGF system may have a potential therapeutic target in reducing the risk of developing and progression of vascular complications in DM patients. Hence, future studies focusing on the role of IGF on DM complications should emphasis on the mechanism of the system to tackle the disease progression and reduce DM.
related complications in large cohort of patients.

5. Author’s Contributions

BB, WT and SA each contributed to the literature search, writing and editing of this review article.

6. Conflicts of interest

The authors declare no conflict of interest.

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