REVIEW ARTICLE

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The Role of Insulin-like Growth Factor 1, Pro-neurotensin and 25-Hydroxy Vitamin D3 in Type 2 Diabetes Mellitus: Metabolic and Pathophysiological links

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Abstract

Type 2 diabetes mellitus (T2DM) is a complex disease involving both environmental and genetic contributing factors. T2DM and metabolic syndrome are associated with decreased insulin like growth factor 1 (IGF-1) and vitamin D3. Several studies reported a positive influence of IGF-I on glucose homeostasis exerting insulin-like biological effects. In addition, vitamin D3 has been demonstrated to stimulate insulin secretion from the pancreatic β-cells and modulate β-cell growth and differentiation. Indeed, low vit D3 level has emerged as a risk factor for insulin resistance and T2DM. The relationship between vitamin D deficiency and insulin resistance could develop through inflammation. Pro-neurotensin (pro-NT) is the stable precursor of neurotensin that is secreted by intestinal neuroendocrine cells in response to food ingestion, facilitating lipid absorption with a direct influence on blood glucose control being co-secreted with other gastrointestinal hormones, such as glucagon-like peptide-1 (GLP-1). Elevated pro-NT levels were linked with an increased risk of T2DM and cardiovascular disease and have been reported to predict future development of obesity and diabetes mellitus. Therefore, IGF-I, vitamin D3 and pro-NT can be regarded as promising biomarkers for early diagnosis and treatment of T2DM and can also predict future development of diabetic complications.

Keywords: IGF-I; pro-NT; vitamin D3; T2DM.

1. Introduction

The increasing incidence of type 2 diabetes mellitus (T2DM) worldwide is a major health concern. In 2013, 8.3% of people were affected with diabetes worldwide **(International Diabetes Federation, 2013)**. T2DM has a long asymptomatic pre-clinical phase during which time, 20–30% of patients develop complications such as retinopathy, cardiovascular disease, neuropathy, and nephropathy **(Sinnott et al., 2015; Bell, 2023)**. Therefore, early detection followed by lifestyle modification and/or pharmacotherapy can delay or arrest disease progression **(Knowler, 2002; American diabetes association, 2009)**.

The International Diabetes Federation (IDF) listed Egypt among the world top 10 countries in the number of diabetic patients. This number in the Middle East and North Africa (MENA) region is expected to grow by 96% from year 2013 to 2035 or from 34.6 million to 67.9 million. In Egypt, diabetes prevalence has been reported to increase rapidly within a relatively short period with an expected higher prevalence by 2035 **(Jain and Saraf, 2010; Whiting et al., 2011; International**

Diabetes Federation, 2013).

T2DM is an age-related chronic disease associated with a reduction in skeletal muscle strength and mass and an increase in body fatness and blood inflammatory markers **(Donath and Shoelson, 2011)**. The reduction of muscle mass leads to impaired physical function, high risk of falls and fractures, and worsening of glycemic control, since skeletal muscle mass represents the largest insulin-sensitive tissue of the body **(Kalyani et al., 2014)**. Moreover, the concomitant increase of fat mass is directly associated with insulin resistance and chronic inflammation in T2DM patients **(Shoelson et al., 2006; Donath and Shoelson, 2011)**.

2. Epidemiology of T2DM

The prevalence of diabetes is steadily increasing everywhere, most markedly in the world's middle-income countries. Globally, an estimated 422 million adults were living with diabetes in 2014, compared to 108 million in 1980. The global prevalence (age-standardized) of diabetes has nearly doubled since 1980, rising from 4.7% to 8.5% in the adult population. This dramatic rise is largely due to the rise in T2DM and factors driving it including overweight and obesity. Over the past decade, diabetes prevalence has risen faster in low- and middle-income countries than in high-income countries, and it is expected to grow to 592 million in 2035 **(Bruno et al., 2022)**. Diabetes caused 1.5 million deaths in 2012 **(Cita and Yuanita, 2022)**. In the Middle East and North Africa region, more than 35.4 million people have diabetes and by 2040, this number is expected to rise to 72.1 million **(Abdelhamid et al., 2022)**.

After a marked increase over the last three decades, the prevalence of T2DM has now reached epidemic proportions, with almost 400 million adult cases throughout the world **(Muscogiuri et al., 2022)**. It is one of the leading causes of death and disability **(Yefet et al., 2020)**. Diabetes tends to affect males more than females since more males are diagnosed with T2DM. In addition, males are diagnosed at lower body mass index (BMI) levels than females **(Lee et al., 2022)**.

T2DM is a fast-growing health problem in Egypt with a significant impact on morbidity, mortality, and health care resources. There were over 7.8 million cases of diabetes in Egypt in 2015 **(Youssef et al., 2022)**. The prevalence of T2DM in Egypt is around 15.6% of all adults aged 20 to 79, with an annual death of 86478 related to diabetes (**Abd-El-Fatah et al., 2020)**. The International Diabetes Federation has identified Egypt as the ninth leading country in the world for the number of patients with T2DM. The prevalence of T2DM in Egypt was almost tripled over the last 2 decades. This sharp rise could be attributed to either an increased pattern of the traditional risk factors for T2DM such as obesity, physical inactivity and change in eating pattern or other risk factors unique to Egypt. These include increased exposure to environmental risk factors like pesticides and increased prevalence of chronic hepatitis C **(Hegazi et al., 2015)**.

3. Diagnosis of T2DM

T2DM is diagnosed when hemoglobin A1c (HbA1c) is ≥ 6.5% or fasting serum glucose (FSG) is ≥ 126 mg/dl or 2-hour postprandial serum glucose is ≥ 200 mg/dl during an oral glucose tolerance test or a random serum glucose is ≥ 200 mg/dl plus symptoms of diabetes (**Khare et al., 2022)**.

4. Pathogenesis of T2DM

T2DM involves at least two primary pathogenic mechanisms **(Galicia-Garcia et al., 2020)**. First, a progressive decline in pancreatic islet cell function results in reduced insulin secretion and inadequate suppression of glucagon secretion. Second, peripheral insulin resistance (IR) resulting in a decrease in the metabolic responses to insulin. The natural history of T2DM begins with normal glucose tolerance and IR. Insulin resistance is defined as a decreased ability of insulin to perform its biological functions in adipose tissue, liver, and muscles. The IR observed in skeletal muscle is particularly important, as under normal physiological conditions, this tissue is responsible for more than 80% of whole-body insulin-mediated glucose disposal **(Reddel et al., 2022)**.

The consequences of IR at the tissue level include reduced glucose uptake into peripheral sites including adipose tissue and muscles, combined with excessive glucose output by the liver leading to hyperglycemia. Also, glucagon rise during fasting is not suppressed with hyperglycemia. In the IR state, the pancreas is able to initially compensate for IR through increased production of insulin from the pancreas, commonly referred to as hyperinsulinemia. With time, however, there is a progression to impaired glucose tolerance, and

eventually, the pancreatic β-cells are unable to maintain increased insulin secretion leading to T2DM development **(Al-Suhaimi et al., 2022)**.

One of the primary mechanisms that control insulin secretion following the ingestion of food is the gut secretion of incretins, namely, glucagon-like peptide 1 and glucagon inhibitory peptide. Approximately 50% of the insulin secreted acutely after a meal is absorbed is attributable to these molecules; however, their insulin trophic effects are progressively decreased during the development of T2DM. This decrease is attributable to a synergistic combination of decreased incretin secretion, raised circulating levels of the enzyme responsible for its breakdown, dipeptidyl peptidase 4, and resistance to incretin signaling in pancreatic β cells. Indeed, incretins potentiate glucose stimulated secretion of insulin via binding to specific G- protein coupled receptors that activate the adenylyl cyclase pathway **(Holst, 2021)**.

There have been many factors implicated in the pathogenesis of T2DM. Some of the cellular, molecular, and biochemical abnormalities include impaired insulin intracellular signaling, reduced insulin-stimulated glucose uptake, decreased hexokinase II expression and activity, diminished glycogen synthase activity, decreased pyruvate dehydrogenase activity, and impaired mitochondrial function. Lipotoxicity, glucotoxicity, and low-grade inflammation also have been described in the pathogenesis of T2DM **(Mengeste et al., 2021)**.

The pathophysiology of T2DM varies with tissues or organs. The contribution of each tissue or organ to T2DM is summarized in **Figure 1**. Several events have been reported to be associated with T2DM include a defect in insulin-mediated glucose uptake in skeletal muscle, a disruption of secretory function of adipocytes, a dysfunction of pancreatic β-cells, impaired sensing and response to hyperglycemia in the central nervous system (CNS), an excessive accumulation of lipids, and impaired fatty acid oxidation due to obesity, physical inactivity, and genetic predisposition **(Lin and Sun, 2010)**.

4.1. Role of Insulin-like growth factor 1 (IGF-1) in T2DM pathogenesis

Insulin like growth factors (IGFs) are anti-catabolic and pro-anabolic agents that act on a multitude of cell types. IGFs are members of a family of insulin related peptides that include relaxin and several peptides isolated from lower invertebrates **(Semaniuk et al., 2021)**. IGF is a complex of two peptides, IGF-1 and IGF-2. IGF-1 is a cytokine which is a facilitator and moderator of the GH **(Costales and Kolevzon, 2016)**. It is a small peptide consisting of 70 amino acids with a molecular weight of 7649 Da **(Tomašovský et al., 2023)**.

Like insulin, IGF-1 has an A and B chain connected by disulphide bonds. The C peptide region has 12 amino acids. The structural similarity to insulin explains the ability of IGF-1 to bind (with low affinity) to the insulin receptor. IGF-1 is an important GH, mediating the protein anabolic and linear growth promoting effect of pituitary GH. It has a GH independent growth stimulating effect, which with respect to cartilage cells is possibly optimized by the synergistic action with GH **(Laron, 2001)**.

IGF-1 is a polypeptide hormone with endocrine, paracrine, and autocrine effects, which shares structural homology (>60 %) with IGF-2 and proinsulin **(Tomašovský et al., 2023)**. It is mainly produced by the liver (accounting for ≈75 % of circulating IGF-1) secondary to GH and insulin endocrine stimulation in the liver **(Liu et al., 2014)**. Conversely, IGF-1 acts to provide an inhibitory feedback signal on GH secretion in the hypothalamus by stimulating somatostatin production in the pituitary **(Al-Massadi et al., 2022)**. IGF-1 is also produced locally in all bodily tissues **(Higashi et al., 2019)**. IGF-1 availability is tightly regulated by IGFBPs, which act by increasing IGF-1 half-life by forming a tertiary complex with acid-labile subunit and IGFBP3, however blocking its binding to IGF-1R. IGFBPs can also act to guide IGF-1 to specific tissues, or even to inhibit or potentiate IGF-1 actions by acting as an independent substrate for the IGF-1R and/or other specific membrane, intracellular or nuclear receptors **(LeRoith et al., 2021)**.

IGF-I has an almost 50% amino acid sequence homology with insulin and elicits nearly the same hypoglycemic response. Several studies have investigated the effect of IGF-I on insulin sensitivity and its relation to T2DM. Large longitudinal studies, including the National Health and Nutrition Examination Survey (NHANES) III, reported a higher risk of insulin resistance, metabolic syndrome (MetS), and T2DM in subjects with low IGF-I serum concentrations or low IGF-I/IGFBP-3 ratio. Previous studies showed that low and high baseline IGF-I serum concentrations were

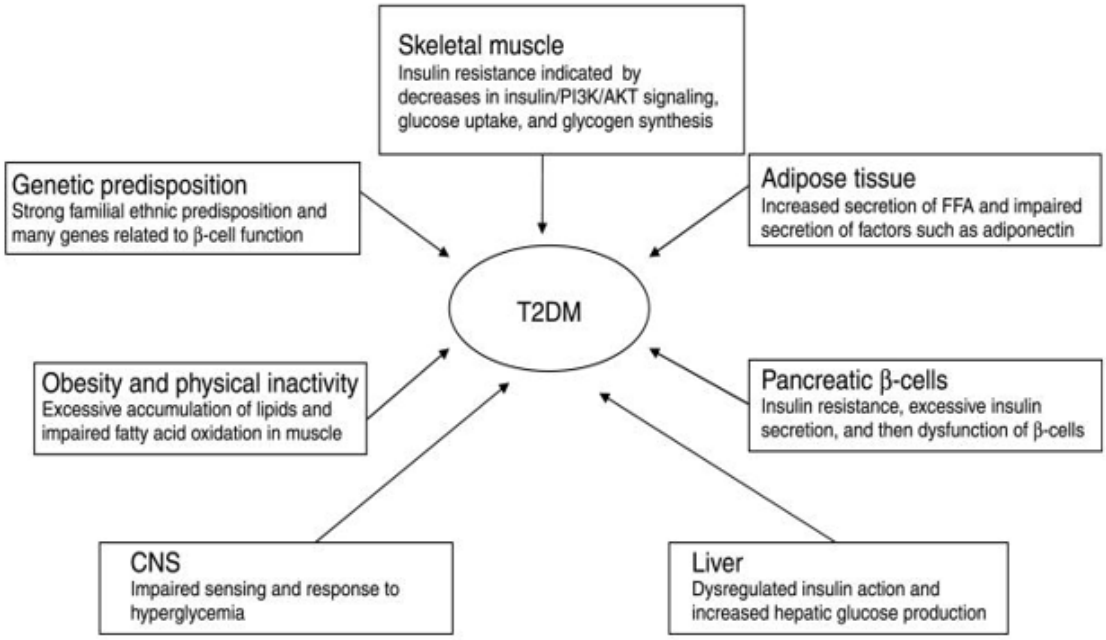

Figure 1. The contribution of different tissues and organ in the pathophysiology of T2DM. PI3K: Phosphatidylinositol-3-kinase; AKT: Protein kinase B; FFA: Free fatty acid **(Lin and Sun, 2010)**.

both related to a higher risk of developing T2DM. This U-shaped association seems to be likely in face of a higher prevalence of MetS or T2DM in patients with GH deficiency, a state of low IGF-I levels, as well as with acromegaly, a disease characterized by high IGF-I levels, although endogenous GH secretion may confound short-term glucose homeostasis in these patients. Therefore, a U-shaped relation was also hypothesized to exist between IGF-I levels and insulin sensitivity as precursor to manifest T2DM **(Castigliego et al., 2011)**.

Moreover, animal models showed that a deletion of hepatic IGF-I production, resulting in 80% reduced IGF-I levels, hyperinsulinemia and abnormal glucose clearance. **Friedrich et al. (2012)** have reported a negative correlation between IGF-I levels and insulin resistance measured by the homeostasis model assessment of insulin resistance (HOMA-IR).

Insulin-like biological effects of IGF-1 have been previously reported **(Kiss et al., 2019)**. IGF-1 effectively stimulates glucose uptake into muscle and increases whole body glucose metabolism. In addition, IGF-1 inhibits protein degradation, stimulates protein synthesis, and decreases levels of free fatty acids. IGF-1 also directly inhibits Beta - cell insulin secretion **(Liu et al., 2014)**. In these respects, IGF-1 and insulin are similar although However, IGF-1 and insulin differ in that the former suppresses pituitary GH and insulin does not and the latter (insulin) suppresses the synthesis and release of IGFBP1 from the liver. They also differ dramatically in the fact that IGFs, and not insulin, are bound by a family of specific binding proteins that alter their bioavailability and that may determine some tissue specificity of action. Thus, based on its pattern of action and its unique cognate receptor, IGF-1 would seem to be an excellent candidate for use in states of altered carbohydrate metabolism **(Lin et al., 2023)**.

Early studies on the structure and function of both insulin and IGF-1 and their respective cognate cell surface membrane receptors revealed remarkable homology at the level of both the peptides and the receptors **(Lin et al., 2023)**. Indeed, both insulin and IGF-1 also revealed remarkable homology at the level of their respective cognate cell surface membrane receptors with each ligand binding to the other ligand's receptor although with much lower affinity. One potential reason to consider IGF-1 in the therapy of DM relates to the prolonged half-life of IGF-1 that results from the specific binding of IGF-1 to binding proteins. This is distinctly different from the short half-life of insulin following endogenous secretion or intravenous injection **(Stanley et al., 2021)**.

In addition, the ability of IGF to suppress

with different potencies for the different effects.

endogenous insulin secretion while stimulating glucose uptake in peripheral tissues offers the possibility that IGF 1 could substitute for insulin in states of insulin resistance from the most severe to that present in T2DM. The ability of IGF-1 to bypass insulin resistance requires that IGF-1 works through different pathways than insulin, at least in critical insulin-responsive tissues **(Li et al., 2022)**.

4.1.1. The IGF-1 receptor

The human IGF-1R (type 1 receptor) is the product of a single copy gene spanning over 100 kb of genomic DNA at the end of the long arm of chromosome 15q25–26. The gene contains 21 exons, and its organization resembles that of the structurally related insulin receptor **(Castigliego et al., 2011)**. IGF-1R gene is expressed by almost all tissues and cell types during embryogenesis. In the liver, the organ with the highest IGF-1 ligand expression, IGF-1R mRNA is almost undetectable, possibly because of the "downregulation" of the receptor by the local production of IGF-1 **(Xu et al., 2020)**.

The IGF-1R is a heterotetramer composed of two extracellular spanning α subunits and transmembrane β subunits. The α subunits have binding sites for IGF-1 and are linked by disulphide bonds. The β subunit has a short extracellular domain, a transmembrane domain, and an intracellular domain. The intracellular part contains a tyrosine kinase domain, which constitutes the signal transduction mechanism as shown in **Figures 2** and **3 (Nagao et al., 2021)**.

Like the insulin receptor, the IGF-1 receptor undergoes ligand induced autophosphorylation leading to the recruitment and phosphorylation of receptor substrates such as insulin receptor substrate (IRS) and src homology domain (Shc) proteins **(Nagao et al., 2021)**. Shc activates the Ras-mitogen activated protein kinase (MAPK) pathway controlling cellular proliferation and gene transcription, whereas IRS proteins mostly activate the phosphatidylinositol-3 kinase (PI3K)-Akt pathway by recruiting and activating PI3K, leading to the generation of second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3). Membrane-bound PIP3 recruits and activates phosphoinositide-dependent kinase-1 (PDK-1), which phosphorylates and activates Akt. The latter mediates most of insulin's metabolic effects, plays a role in the control of cell cycle and survival **(Laron, 2001)**.

4.1.2. IGF-1 metabolic effect

At first glance, IGF-1 has historical fame for being a growth and differentiation factor, however, several growth-unrelated actions have been recently unraveled. A growing body of evidence suggests the involvement of IGF-1 in metabolism coordination. IGF-1, GH and insulin conform a finely regulated axis that inform cells about the nutritional status of the organism so that they can either undergo apoptosis/senescence/quiescence or, to the contrary, grow and differentiate **(Macvanin et al., 2023)**. Parallel to this signal, potent protective effects have been attributed to this hormone. Thus, besides signaling abundance and growth, it provides protection against the possible deleterious effects of augmented metabolism. Likewise, anti-inflammatory actions of IGF-1 can be regarded as a crucial factor protecting tissues from the deleterious effects of pro-inflammatory mediators in chronic disorders such as obesity **(Lathigara et al., 2023)**.

It has been well established that pro-inflammatory cytokines produced by the adipose tissue in obesity affect normal nutrition-related signaling, establishing the progression to MetS and ultimately to T2DM. Additionally, it is now known that pro-inflammatory cytokines also affect IGF-1 intracellular signaling by phosphorylating serine residues on insulin related substrate (IRS) molecules and hence impeding their binding to IGF-1R **(Lathigara et al., 2023)**. This results in a blockade of IGF-1 beneficial actions. Under this scenario, a correlation between IGF-1 and MetS can be established **(Masliukov, 2023)**.

Moreover, in pathophysiological states including increased insulin resistance, the insulin/IGF-1 hybrid receptor number is changed significantly, thus potentially abrogating the chance for IGF-1 to alter glucose metabolism. IGF-1 possesses both GH-like actions and insulin-like actions **(Masliukov, 2023)**. However, GH can also exert metabolic actions independent from IGF-1 generation in the liver via activation of PI3K and IRS pathways. In this way, GH and insulin act in symphony with IGF-1 to produce a coordinated response **(Aguirre et al., 2016)**.

regulating glucose transport, lipid synthesis, gluconeogenesis, and glycogen synthesis. Akt also

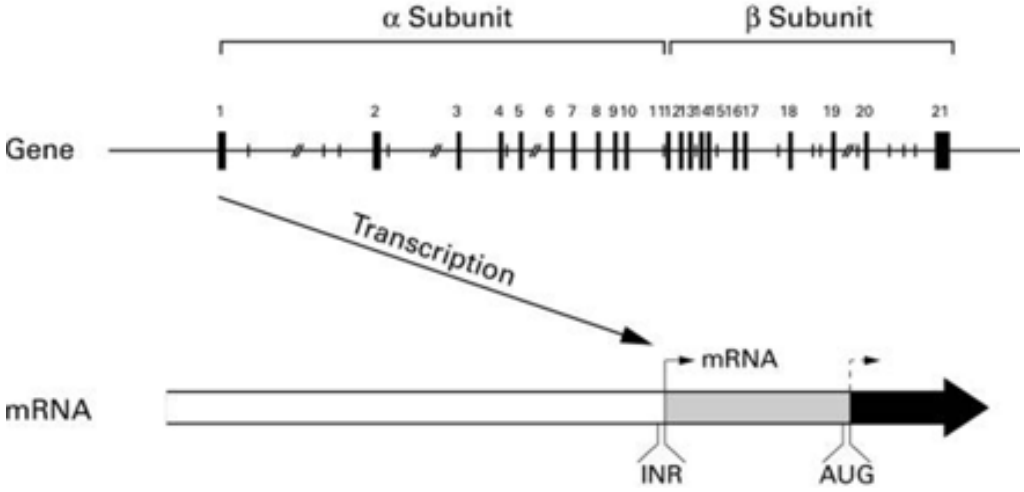

Figure 2. IGF-1 receptor gene and mRNA **(Laron, 2001)**

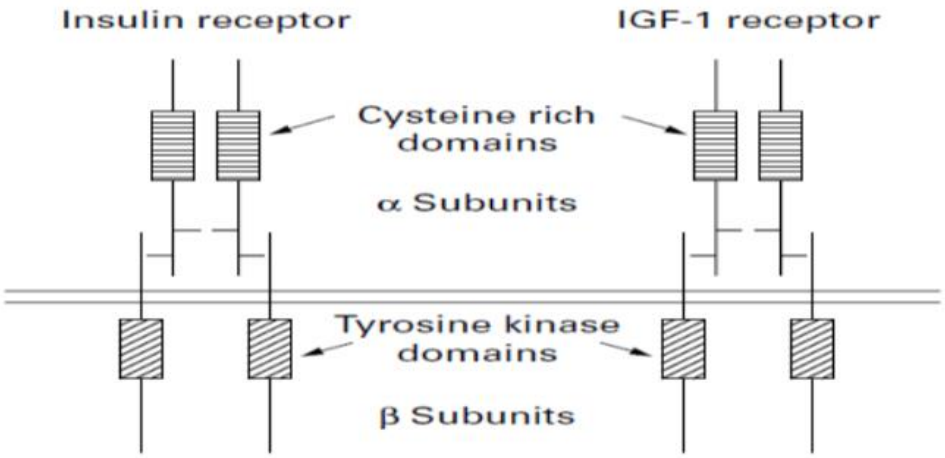

Figure 3. Resemblance between the insulin and IGF-1 receptors **(Laron, 2001)**

4.1.3. IGF-1 and carbohydrate metabolism

IGF-1 can promote glucose uptake in certain peripheral tissues in the magnitude of 4–7 % from that of insulin **(Hernández et al., 2022)**. In addition, exogenous IGF-1 administration has been shown to reduce serum glucose levels, not only in healthy individuals, but also in those with insulin resistance, T1DM, and T2DM **(Aguirre et al., 2016)**.

4.1.4. IGF-1 and lipid metabolism

IGF-1 promotes preadipocyte differentiation, however, as preadipocytes differentiate, they stop expressing IGF-1Rs, delegating such functions now to insulin receptors, which increase in number significantly. Thus, in the adipose tissue, only at high concentrations can stimulate glucose transport via the insulin receptor **(Zorina et al., 2023)**. On the other hand, insulin is a potent stimulant of lipid synthesis, antagonizing TG breakdown. An increase in FFA efflux from adipose tissue to liver can result in insulin resistance in the liver and GH is known to antagonize insulin action by this means **(Aguirre et al., 2016)**.

IGF-1 promotes fatty acid transport in muscle and its inhibition causes severe consequences like insulin resistance and eventual diabetes **(Kuchay et al., 2022)**. This is due to the uptake of circulating FFAs by the liver, which then interferes with insulin and IGF-1 signaling, eventually leading to hepatic steatosis. Therefore, the two major effects that are enhanced by IGF-1 are FFA use by muscle

physiological IGF-1 concentrations are not effective in stimulating changes in lipid synthesis or lipolysis, lipogenesis in fat. Given the augmented FFA use by muscle and insulin signal reinstitution by IGF-1, there is a marked reduction in total FFA flux. **Figure 4** summarizes some of the metabolic effects that IGF-1 and insulin exert on kidney, brain, skeletal muscle, liver, adipose tissue, and pancreas **(Aguirre et al., 2016)**.

4.2. Role of pro-NT in T2DM pathogenesis

Neurotensin (NT) is an intestinal peptide released after fat ingestion, which regulates appetite and facilitates lipid absorption. Elevated plasma level of its stable precursor pro-NT predicts future development of T2DM, obesity, cardiovascular disease (CVD), and premature mortality **(Barchetta et al., 2018a, 2018b; Barchetta et al., 2022)**.

NT is a 13 amino-acids peptide actively involved in the regulation of appetite, caloric intake, and energy balance, acting both as a neurotransmitter and a gut peptide. In the brain, NT acts as a neurotransmitter by modulating the leptin-mediated food intake and exerts anorexigenic effects via its specific receptor, regulating hedonic feeding behavior, and is also involved in pituitary hormone secretion, nociception, thermoregulation, and modulation of dopaminergic transmission **(Tyler-McMahon et al., 2000; Cimini et al., 2022)**. In the periphery, NT is secreted by intestinal neuroendocrine cells in response to food ingestion, facilitating lipid absorption through the gut mucosa **(Li et al., 2016; Barchetta et al., 2021)**. Of note, NT is co-secreted with other gastrointestinal hormones, such as glucagon-like peptide-1 (GLP-1) with a direct influence on blood glucose control **(Cimini et al., 2022)**.

Indeed, the overall effects of NT are to increase after meal blood triglyceride (TG) concentration, and to promote bile acids reabsorption and enterohepatic circulation. NT contributes to high fat diet induced obesity by facilitation of intestinal fat absorption. pro-NT increases after an oral lipid load and is significantly related to the rise in post-ingestion plasma TG levels. Increased fasting levels of pro-NT have been associated with the presence and development of dysmetabolic conditions, such as obesity, T2DM, insulin sensitivity, non-alcoholic fatty liver disease (NAFLD) **(Mohamed et al., 2022)**, and cancer as well as increased cardiovascular mortality **(Barchetta et al., 2021)**. and GH suppression. These two actions result in a and IGF-1 signaling. Such improvement promotes NT may be considered as a disease mediator and a promising therapeutic target for the prevention and treatment of dysmetabolic conditions.

Barchetta et al. (2021) reported that elevated plasma pro-NT levels could predict bodyweight gain and impaired β-cell secretion in response to insulin resistance later in life. Thus, pro-NT may represent a marker of susceptibility to metabolic impairment in the presence of obesity. Increased pro-NT concentration has been reported to be associated with low high-density lipoprotein (HDL) and high TG levels. It has been shown that earlier age of obesity onset and longer cumulative exposure to obesity are associated with T2DM risk, even more than BMI itself. The presence of elevated pro-NT levels may, at least in part, contribute to the development of impaired insulin secretion/sensitivity later in life **(Barchetta et al., 2021)** and have been reported to be associated with T2DM risk **(Melander et al., 2012; Januzzi et al., 2016)**.

4.2.1. Pro-NT metabolic effects

The key metabolic actions of neurotensin include digestion and metabolism of fat. It can be speculated that high plasma pro-NT in the fasting state may be a result of compensatory increase in secretion of NT due to resistance to the actions of NT at the level of either its receptors or downstream of them, i.e., NT resistance **(Melander et al., 2012)**.

Another finding was that glucose significantly decreased after fat ingestion. One explanation for this finding is that neurotensin acts synergistically with GLP1 and peptide YY in the distal small intestines to decrease palatable food intake and to inhibit gastric emptying, thus leading to lower glucose concentration. As a second explanation, it is assumed that glucose production by the liver is reduced after fat ingestion, which could reduce glycemia after lipid ingestion **(Fawad et al., 2020)**.

The major candidate receptor linking NT to cardiovascular disease and diabetes is the NT receptor 3, a protein that sorts various luminal proteins from the Trans -Golgi. Previous studies identified genetic variation of the NT receptor 3 as one of the strongest common susceptibility genes for coronary artery disease in the genome, an effect mediated through elevated levels of low-density lipoprotein cholesterol (LDL-C). In addition, NT

Thus, besides representing a validated marker of metabolic and cardiovascular diseases in humans,

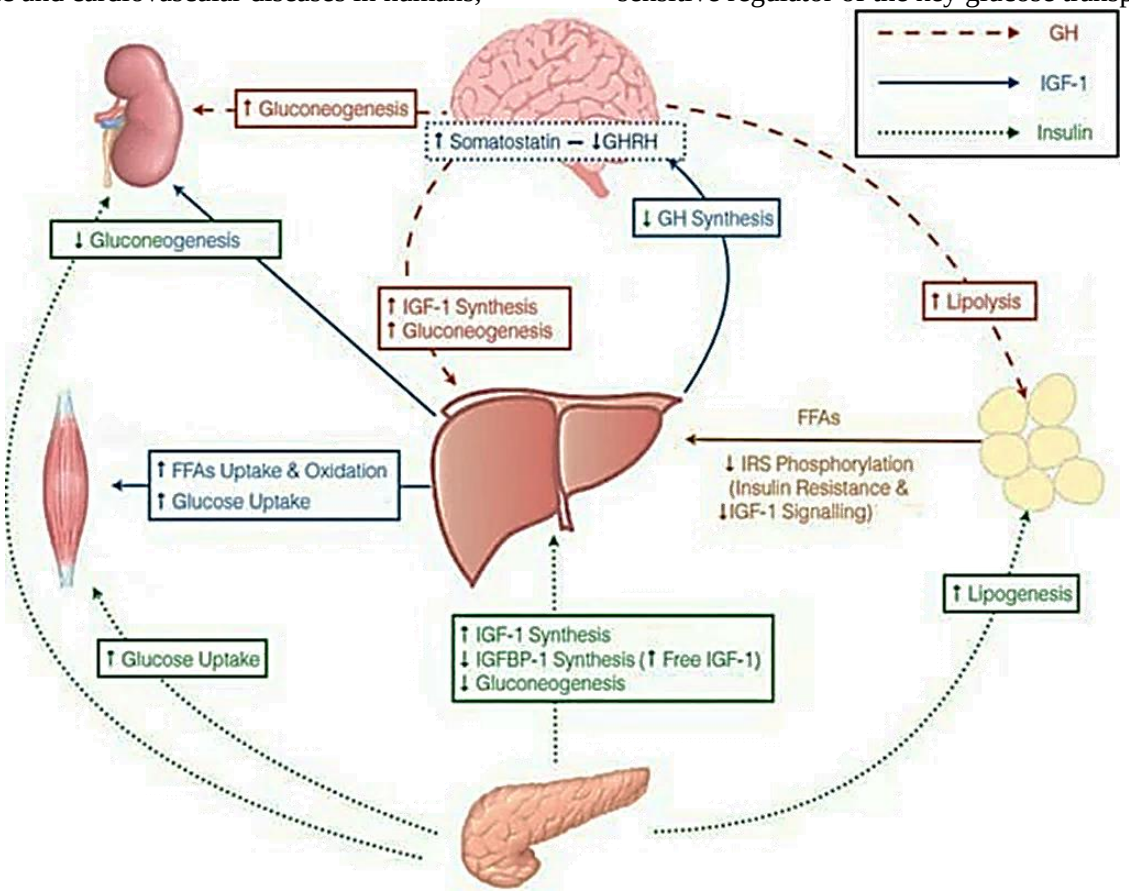

Figure 4. Metabolic effects of IGF-1, GH, and insulin under physiological conditions on their target organs **(Aguirre et al., 2016)**. GH = growth hormone, GHRH = growth hormone releasing hormone, FFA = free fatty acid, IRS = insulin receptor substrate, IGF-1 = insulin-like growth factor 1, IGBBP-1 = insulin-like growth factor binding protein 1.

receptor 3 has been suggested to be an insulin-sensitive regulator of the key glucose transporter in muscle and adipose tissue, i.e., glucose transporter 4 (GLUT4), suggesting a role of the neurotensin system not only in metabolism of LDL-C and coronary artery disease but also in insulin resistance and diabetes development. In fact, fasting insulin concentration was one of the strongest correlates of pro-NT **(Melander et al., 2012; Fawad et al., 2019)**.

Collectively, NT can affect several pathophysiological mechanisms, partially overlapping those occurring in T2DM and MetS; among them, altered secretion pattern of gut peptide hormones, including amylin, ghrelin and glucose-dependent insulinotropic polypeptide (GIP), enhanced intestinal fat uptake and central storage in the liver which in turn contributes to obesity, NAFLD, diabetes and CVD at high levels of fat intake **(Cimini et al., 2022; Fawad et al., 2020)**.

4.3. Role of Vitamin D3 in pathogenesis

Vitamin D can be endogenously synthesized under ultraviolet B radiation in the skin, or ingested through dietary supplements and dietary sources, which include food of animal and plant origin, as well as fortified foods. Vitamin D is mainly found in two forms, D3 (cholecalciferol) and D2 (ergocalciferol) **(Holick, 2009, 2011)**. Vitamin D2 and vitamin D3 are chemically similar and are both well-absorbed in the gut. However, they differ significantly in their sources **(Sempos et al., 2012)**. Another way that vitamin D3 differs from vitamin D2 is in its bioavailability (the proportion of a drug that enters the blood stream) and half-life (a measure of the amount of time a drug remains in circulation) **(Lehmann et al., 2013)**.

Vitamin D made in the skin or ingested in the diet is biologically inert and requires 2 successive hydroxylations first in the liver on carbon 25 to form 25-hydroxyvitamin D (25(OH)D), and then in the kidney for a hydroxylation on carbon 1 to form the biologically active form of vitamin D, 1,25-

of T2DM

is considered the best marker for assessing vitamin D status. It has been postulated that 25(OH) D of <20 ng/mL is considered to be vitamin D deficiency, whereas a 25(OH) D of 21-29 ng/mL is considered to be insufficient. The goal should be to maintain both children and adults at a level >30 ng/mL to take full advantage of all the health benefits that vitamin D provides **(Holick, 2009)**.

Vitamin D3 has proven superior to vitamin D2. Not only does vitamin D3 stay in the body longer, but some studies suggest that it also raises the vitamin D level in the bloodstream 87% more than vitamin D2 **(Tripkovic et al., 2012)**. Vitamin D deficiency has been considered as an increasing global concern threatening public health. It affects almost 50% of the population worldwide **(Nair and Maseeh, 2012)**. Both vitamin D2 and D3 can be used to treat this, with vitamin D3 generally being the preferred choice **(Tripkovic et al., 2012)**.

Beyond its use in treating vitamin D deficiency, vitamin D3 may offer health benefits to certain people without such deficiency. Recent studies suggest that vitamin D3 may help lower blood pressure in people with hypertension and vitamin D deficiency as well as certain groups of people with hypertension only. Previous study showed that vitamin D3 was able to significantly reduce systolic (upper) blood pressure in people over the age of 50 as well as those with obesity **(He and Hao, 2019)**. Moreover, vitamin D3 has been reported to significantly reduce the incidence of hip fractures in nursing home residents aged 70 and over. In addition, low-dose vitamin D3 (400 IU) also increased bone mass density in the femoral (thigh) bone **(Geddes and Inderjeeth, 2013)**.

The main biological role of vitamin D is the regulation of calcium homeostasis and bone formation. However, its association with diabetes and cardiovascular diseases have also been studied **(Afarideh et al., 2016)**. Vitamin D also plays a crucial role in the regulation of the anti-microbial activity via the expression of vitamin D receptor (VDR) in a variety of immune system cells including neutrophils, macrophages, TCD4+, TCD8+ and B-cells. Vitamin D reduces the production of pro-inflammatory cytokines, elevates anti-inflammatory responses and participates in wound-healing processes, insulin resistance prevention and induction of VDR expression **(Afarideh et al., 2016; Esteghamati et al., 2015)**.

dihydroxyvitamin D (1,25(OH)2D). The measurement of the circulating levels of 25 (OH) D **Clarke, 2011)**. **Pittas et al. (2007)** demonstrated that insufficient vitamin D and calcium appears to hinder glycemic control and that supplementing both nutrients may be necessary to optimize glucose metabolism. Vitamin D has been reported to improve glucose tolerance and insulin resistance **(Parekh et al., 2010)**.

There is growing evidence that vitamin D deficiency leads to reduced insulin secretion, insulin resistance and could be a contributing factor in the development of both type 1 and type 2 diabetes. First, the β-cell in the pancreas that secretes insulin has been shown to contain VDRs as well as the 1 α hydroxylase enzyme **(Bland et al., 2004)**. 1,25(OH)2D stimulates the pancreatic β-cell to secrete insulin. The relationship between vitamin D deficiency and insulin resistance could develop through inflammation, as vitamin D deficiency is associated with increased inflammatory markers. In addition, genetic polymorphisms of vitamin D related genes may predispose to impaired glycemic control and T2DM. Previous studies showed an association between low serum 25(OH)D3 concentration and an increased risk for MetS and T2DM. This may be partly explained by an increased fat mass **(Lips et al., 2017)**.

The vitamin D receptor is expressed in many organs including pancreatic β-cell **(Bouillon et al., 2008)**. 1,25(OH)2D3 has been reported to increase insulin secretion from pancreatic islets. The increased secretion may also be caused by a higher intracellular calcium. In addition, the active vitamin D metabolite may modulate β-cell growth and differentiation. Vitamin D deficiency causes secondary hyperparathyroidism with the high parathyroid hormone (PTH) concentration causing glucose intolerance **(Takiishi et al., 2010)**.

5. Diabetic complications

It is estimated that half of patients with diabetes are unaware of their disease and are thus more prone to developing diabetic complications **(Papatheodorou et al., 2018)**. People with T2DM are at increased risk of many complications, which are mainly due to complex and interconnected mechanisms such as hyperglycemia, IR, low-grade inflammation and accelerated atherogenesis. Cardio-cerebrovascular disease is frequently associated with T2DM and may become life

Vitamin D has been linked to several disorders from cancer and heart disease to diabetes **(Thacher and**

progressive, must however be screened and treated in old patients which are globally at high ophthalmologic risk. Diabetic foot is a severe complication secondary to microangiopathy and neuropathy. It may be considered as a super-complication of several complications. Its screening must be done on a routine basis **(Schlienger, 2013)**.

The chronic complications of diabetes are broadly divided into microvascular and macrovascular, with the former having much higher prevalence than the latter. Microvascular complications include neuropathy, nephropathy, and retinopathy, while macrovascular complications consist of cardiovascular disease, stroke, and peripheral artery disease (PAD) which is a common complication and comorbidity of diabetes. Patients with diabetic foot ulcers have coexisting PAD at a proportion of approximately 50% and may suffer from chronic ischemic pain **(Papatheodorou et al., 2018)**.

5.1. Microvascular complications of diabetes

5.1.1. Diabetic retinopathy

Diabetic retinopathy may be the most common microvascular complication of diabetes **(Kropp et al., 2023)**. The risk of developing diabetic retinopathy or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia **(Poonoosamy et al., 2023)**. Retinopathy may begin to develop as early as 7 years before the diagnosis of diabetes in patients with T2DM **(Kollias and Ulbig, 2010)**. Aldose reductase may participate in the development of diabetes complications. Aldose reductase is the initial enzyme in the intracellular polyol pathway. This pathway involves the conversion of glucose into sorbitol. High glucose levels increase the flux of sugar molecules through the polyol pathway, which causes sorbitol accumulation in cells. Osmotic stress from sorbitol accumulation has been postulated as an underlying mechanism in the development of diabetic microvascular complications, including diabetic retinopathy. Cells are also thought to be injured by glycoproteins. High glucose concentrations can promote the nonenzymatic formation of advanced glycosylated end products (AGEs) with subsequent formation of microaneurysms and pericyte loss **(Fowler, 2008)**.

threatening, particularly stroke and heart failure. Retinopathy, which is paradoxically slightly

stimulate free radical production and reactive oxygen species formation. Growth factors, including vascular endothelial growth factor (VEGF), growth hormone, and transforming growth factor β, have also been postulated to play important roles in the development of diabetic retinopathy. VEGF production is increased in diabetic retinopathy, possibly in response to hypoxia. In animal models, suppressing VEGF production is associated with less progression of retinopathy **(Fowler, 2008)**.

Diabetic retinopathy is generally classified as either background or proliferative **(Saini et al., 2021)**. Background retinopathy includes such features as small hemorrhages in the middle layers of the retina. They clinically appear as “dots” and therefore are frequently referred to as “dot hemorrhages.” Hard exudates are caused by lipid deposition that typically occurs at the margins of hemorrhages **(Murugesan et al., 2015)**. Microaneurysms are small vascular dilatations that occur in the retina, often as the first sign of retinopathy. They clinically appear as red dots during retinal examination. Retinal edema may result from microvascular leakage and is indicative of compromise of the blood-retinal barrier. Retinal edema may require intervention because it is sometimes associated with visual deterioration **(Fowler, 2008)**.

Proliferative retinopathy is characterized by the formation of new blood vessels on the surface of the retina and can lead to vitreous hemorrhage. White areas on the retina (“cotton wool spots”) can be a sign of impending proliferative retinopathy. If proliferation continues, blindness can occur through vitreous hemorrhage and traction retinal detachment. Laser photocoagulation can often prevent proliferative retinopathy from progressing to blindness. Therefore, close surveillance for the existence or progression of retinopathy in patients with diabetes is crucial **(Fowler, 2008)**.

5.1.2. Diabetic neuropathy

Diabetic neuropathy is recognized by the American Diabetes Association (ADA) as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes **(Fowler, 2008)**. As with other microvascular complications, risk of

Oxidative stress may also play an important role in cellular injury from hyperglycemia **(Dey and Lakshmanan, 2013)**. High glucose levels can attributes that affect their predisposition to developing such complications **(Candrilli et al., 2007)**.

The precise nature of injury to the peripheral nerves from hyperglycemia is not known but likely is related to mechanisms such as polyol accumulation, injury from AGEs, and oxidative stress. Peripheral neuropathy in diabetes may manifest in several different forms, including sensory, focal/multifocal, and autonomic neuropathies **(Chukwubuzo et al., 2022)**. More than 80% of amputations occur after foot ulceration or injury, which can result from diabetic neuropathy. Because of the considerable morbidity and mortality that can result from diabetic neuropathy, it is important for clinicians to understand its manifestations, prevention, and treatment **(Fowler, 2008)**.

Chronic sensorimotor distal symmetric polyneuropathy is the most common form of neuropathy in diabetes. Typically, patients experience burning, tingling, and electrical pain, but sometimes they may experience simple numbness. Patients with simple numbness can present with a painless foot ulceration, so it is important to realize that lack of symptoms does not rule out presence of neuropathy **(Pafili et al., 2020)**. Physical examination reveals sensory loss to light touch, vibration, and temperature. Abnormalities in more than one test of peripheral sensation are > 87% sensitive in detecting the presence of neuropathy. Patients also typically experience loss of ankle reflex. Patients who have lost 10-g monofilament sensation are at considerably elevated risk for developing foot ulceration **(Fowler, 2008)**.

Pure sensory neuropathy is relatively rare and associated with periods of poor glycemic control or considerable fluctuation in diabetes control **(Bloomgarden, 2005)**. It is characterized by isolated sensory findings without signs of motor neuropathy. Symptoms are typically most prominent at night. Mononeuropathies typically have a more sudden onset and involve virtually any nerve, but most commonly the median, ulnar, and radial nerves are affected. Cranial neuropathies have been described but are rare. It should be noted that nerve entrapment occurs frequently in the setting of diabetes. Electrophysiological evaluation in diabetic neuropathy demonstrates decreases in both amplitude of nerve impulse and conduction but developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycemia, and some individuals may possess genetic characterized by severe pain and muscle weakness and atrophy, usually in large thigh muscles **(Giha et al., 2022)**.

Several other forms of neuropathy may mimic the findings in diabetic sensory neuropathy and mononeuropathy. Chronic inflammatory polyneuropathy, vitamin B12 deficiency, hypothyroidism, and uremia should be ruled out in the process of evaluating diabetic peripheral neuropathy **(Fowler, 2008)**. Diabetic autonomic neuropathy also causes significant morbidity and even mortality in patients with diabetes **(Bloomgarden, 2005)**. Neurological dysfunction may occur in most organ systems and can by manifest by gastroparesis, constipation, diarrhea, anhidrosis, bladder dysfunction, erectile dysfunction, exercise intolerance, resting tachycardia, silent ischemia, and even sudden cardiac death. Cardiovascular autonomic dysfunction is associated with increased risk of silent myocardial ischemia and mortality **(Fowler, 2008)**.

5.1.3. Diabetic nephropathy

Diabetic nephropathy (DN) is one of the most feared diabetic chronic microvascular complications and the major cause of end-stage renal disease (ESRD). The classical presentation of DN is characterized by hyperfiltration and albuminuria in the early phases which is then followed by a progressive renal function decline. The presentation of diabetic kidney disease (DKD) can vary especially in patients with T2DM where concomitant presence of other glomerular/tubular pathologies and severe peripheral vascular disease can become important confounders. All-cause mortality in individuals with DKD is approximately 30 times higher than that in diabetic patients without nephropathy and a great majority of patients with DKD will die from cardiovascular disease before they reach ESRD. The management of metabolic and hemodynamic perturbations for the prevention and for the delay of progression of DKD is very important **(Sagoo and Gnudi, 2020)**.

5.2. Macrovascular complications of diabetes

The central pathological mechanism in macrovascular disease is the process of

may be useful in identifying the location of nerve entrapment. Diabetic amyotrophy may be a manifestation of diabetic mononeuropathy and is injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of arteries **(King et al., 2005)**.

Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation. The net result of the process is the formation of a lipid-rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction. In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in T2DM **(Pretorius et al., 2018)**. Impaired nitric oxide generation and increased free radical formation in platelets, as well as altered calcium regulation, may promote platelet aggregation. Elevated levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with diabetes. The combination of increased coagulability and impaired fibrinolysis likely further increases the risk of vascular occlusion and cardiovascular events in T2DM (**Fowler, 2008)**.

Diabetes increases the risk that an individual will develop CVD **(Chawla et al., 2016)**. However, the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined. CVD is the primary cause of death in people with either type 1 or type 2 diabetes. Previous studies have shown that the risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk in nondiabetic patients with a history of previous MI **(Viigimaa et al., 2020)**.

These discoveries have led to new recommendations by the ADA and American Heart Association that diabetes be considered a coronary artery disease risk equivalent rather than a risk factor. T2DM typically occurs in the setting of MetS, which also includes abdominal obesity, hypertension, hyperlipidemia, and increased coagulability **(Hayden, 2023)**. These other factors can also act to promote CVD. Even in this setting of multiple risk factors, T2DM acts as an independent atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and disease than men. The presence of microvascular disease is also a predictor of coronary heart events **(Gegunde et al., 2023)**.

Diabetes is also a strong independent predictor of risk of stroke and cerebrovascular disease, as in coronary artery disease. Patients with T2DM have a much higher risk of stroke, with an increased risk of 150-400%. Risk of stroke-related dementia and recurrence, as well as stroke-related mortality, is elevated in patients with diabetes **(Wang et al., 2022)**.

5.3. Correlation of IGF-1, pro-NT, and 25 (OH) D3 with the development of T2DM complications

IGF-1, pro-NT and 25 (OH) D3 have been reported to possess a significant validity in prediction of T2DM complications with 80%, 64% and 64% accuracy, respectively **(Mohammed et al., 2023)**. Combined IGF-1 & 25 (OH) D3 had a significant validity in prediction of T2DM complications with accuracy 77%. In addition, elevated pro-NT levels, yet decreased levels of IGF-1 and 25 (0H) D3 may represent an enhanced susceptibility to metabolic impairment specifically T2DM and can predict complications of T2DM. In this regard, several studies have reported the relation between pro-NT and T2DM with the optimal cutoff value of pro-NT being estimated as a marker for T2DM. Furthermore, a higher cutoff value of pro-NT (>158 pmol/L) has been proved to predict the complications of T2DM with sensitivity and specificity of 64.9% and 63.5%, respectively with an area under the curve of 0.62 (95% confidence interval: 0.50-0.74). Importantly, at a cutoff value of <29.5 ng/ml, IGF-1 has also been proved to predict the complications of T2DM with sensitivity and specificity of 70.3% and 85.7% respectively. Moreover, 25 (OH) D3 had sensitivity and specificity of 67.6% and 62.2%, respectively in predicting the complications of T2DM **(Mohammed et al., 2023)**.

6. Conclusion

T2DM is a complex disease involving both environmental and genetic contributing factors. Potential complications of diabetes and frequent comorbidities include heart disease, stroke, high

risk factor for the development of ischemic disease, stroke, and death. Among people with T2DM, women may be at higher risk for coronary heart associated with risk of T2DM. On the other hand, a positive influence of IGF-I on glucose homeostasis has been confirmed which strengthened the relation between decreased IGF-I and insulin resistance. Furthermore, low blood 25 (OH) D level has emerged as a risk factor for T2DM. Vitamin D supplementation has been hypothesized as a potential intervention to lower diabetes risk. Therefore, these biomarkers could be exploited as therapeutic strategy to achieve better glycemic control and prevent or at least delay the concomitant complications.

Declaration of competing interest

The authors declare no conflicts of interest.

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