ASPI | Afarand Scholarly Publishing Institute; Turkey
ISSN: 2008-2630 Iranian Journal of War & Public Health 2023;15(3):305-310 10.58209/ijwph.15.3.305

Association of Insulin-Like Growth Factor-1 Gene Single Nucleotide Polymorphism rs10860860 with Type 2 Diabetes

ARTICLE INFO

Article Type
Original Research

Authors
AbdulAemah M.A.[1]* *PhD*
Hussein G.M.[2] *PhD*
Hussein N.Y.[3] *PhD*

How to cite this article
AbdulAemah MA, Hussein GM, Hussein NY. Association of Insulin-Like Growth Factor-1 Gene Sing-le Nucleotide Polymorphism rs108-60860 with Type 2 Diabetes. Iranian Journal of War & Public Health. 2023;15(3):305-310.

[1]Department of Clinical Laboratory Sciences, College of Pharmacy, Al-Mustaqbal University, Hillah, Iraq
[2]Department of Clinical Laboratory Sciences, College of Pharmacy, AL-Zahraa University for Women, Karbala, Iraq
[3]Department of Pharmacy, Al-Manara College for Medical Sciences, Amarah, Iraq

Correspondence
Address: Department of Clinical Laboratory Sciences, College of Pharmacy, Al-Mustaqbal University, Hillah, Iraq. Postal Code: -
Phone: 009647802274591
Fax: -
maytham.ahmed@uomus.edu.iq

Article History
Received: May 2, 2023
Accepted: September 18, 2023
ePublished: September 23, 2023

ABSTRACT

Aims One extremely important public health challenge worldwide is diabetes mellitus. Type 2 diabetes mellitus is a rising concern around the globe. Early revealing of Type 2 diabetes mellitus is very significant in that morbidity associated with the condition can be decreased. Studies have proposed that insulin-like growth factor-1 has roles similar to that of insulin. The existing study was implemented to reveal the alliance of single nucleotide polymorphism rs10860860 of the IGF-1 gene with Type 2 diabetes mellitus.

Materials & Methods This case-control study was conducted in Merjan Hospital in Babylon Province, Iraq, in 2022. The available random sampling method selected two groups of healthy individuals (n=50 as control) and Type 2 diabetes mellitus patients (n=158 as study). The serum levels of glucose and zinc were determined by spectrophotometric method. The serum IGF-1 level was estimated using the sandwich ELISA technique. The students' T and Chi-square tests were used to assess data in SPSS 21 software.

Findings The different levels of glucose, zinc, and IGF-1 were significant between the two groups. Genotyping frequencies of the IGF-1 gene deviated from Hardy Weinberg equilibrium in the control group ($\chi 2=9.158$; p=0.002) while were consistent in the study group ($\chi 2=2.482$; p=0.115). The AT genotype was associated with lower odds of Type 2 diabetes mellitus than those of the wild genotype AA.

Conclusion The AT genotype of IGF-1 gene SNP rs10860860 negatively associates with Type 2 Diabetes Mellitus.

Keywords Polymorphism; Insulin-like Growth Factor-1; Diabetes Mellitus, Type 2

CITATION LINKS

[1] Characteristics of diabetic nephropathy patients without diabetic ... [2] Type 2 Diabetes Mellitus and the Association of Candidate Genes in ... [3] Microalbuminuria, other markers of nephropathy and biochemical derangements in type 2 ... [4] Physiological and pathological characteristics of vascular endothelial injury ...[5] Diabetes, hypertension, and cardiovascular disease: clinical insights ... [6] Neurovascular regulation in diabetic retinopathy and ... [7] PAFLP-SSCP: A useful AFLP-based method for informative SNPs ... [8] Diabetes mellitus and its complications in ... [9] The role of DNA methylation in the pathogenesis of ... [10] Insulin-like growth factor 1 (IGF-1): A ... [11] Insulin and its analogues and their affinities for ... [12] Zinc and its regulators in ... [13] Pathophysiology of type 2 ... [14] The dynamic plasticity of insulin production in ... [15] Pancreatic beta-cell electrical activity and insulin secretion: of ... [16] Zinc intake and status and risk of type 2 diabetes mellitus: a systematic ... [17] Evaluation of salivary total protein in insulin dependent diabetes ... [18] Gaps and barriers in the control of blood glucose in people with ... [19] The impact of serum zinc levels on abdominal fat mass ... [20] Assessment of some major minerals and trace elements levels in female patients with type II diabetes ... [21] Zinc deficiency correlates with severity of ... [22] The status of zinc in type 2 diabetic patients and its association ... [23] Serum zinc and magnesium in type-2 ... [24] The effect of adding zinc to vitamin A on IGF-1, bone age and linear ... [25] Effects of zinc supplementation on diabetes mellitus: a systematic ... [26] Effect of zinc supplementation on GH, IGF1, IGFBP3, OCN, and ALP ... [27] Ramipril can alleviate the accumulation of renal mesangial matrix in rats with diabetic nephropathy ... [28] Insulin like growth factor 1 is linked to higher cardiovascular risk score in adults with type 2 ... [29] Insulin-like growth factor-1 is a negative modulator ... [30] Association between serum IGF-1 and ... [31] Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their ... [32] Insulin-like growth factor 1 and insulin-like growth factor–binding protein 3 in relation to the risk of type 2 diabetes mellitus: ... [33] IGF-I and the endocrinology ... [34] Role of insulin-like growth factor-1 and growth hormone in growth inhibition ... [35] An insulin-like growth factor-I gene polymorphism modifies the risk of ... [36] Impact of Hardy Weinberg equilibrium deviation on allele-based risk effect ... [37] Association of IGF-I gene polymorphism with diabetic nephropathy ...

Introduction

The metabolic ailment renowned as diabetes mellitus (DM) is a set of illnesses. It is defined by chronic hyperglycemia in a fed or a state of fasting and turbulences in carbohydrate, lipid, and protein metabolism resulting from faults in insulin deed and/or insulin secretion or both [1]. Type 2 Diabetes Mellitus (T2DM) is undeniably among the most prevalent metabolic conditions on a global scale. Its onset predominantly arises from a dual interplay of factors: malfunctioning insulin secretion by pancreatic β-cells and the resistance of insulin-sensitive tissues towards insulin [2]. The World Health Organization (WHO) defines diabetes mellitus as a persistent metabolic disorder marked by heightened blood glucose levels, gradually harming the heart, blood vessels, eyes, kidneys, and nerves over time.

Based on the International Diabetes Federation, it impacts nearly 1 in 11 adults globally, with type 2 diabetes mellitus influencing over 90 percent of them [3]. Diabetes mellitus has emerged as a significant threat, posing risks to the well-being and lives of individuals on a global scale. The severe implications of DM primarily manifest in its capacity to trigger extensive vascular issues [4]. For instance, individuals diagnosed with T2DM face double the risk of cardiovascular disease compared to the general population, resulting in a notably unfavorable prognosis [5]. Moreover, approximately one-third of diabetic patients experience diabetic retinopathy, significantly impacting their overall health and quality of life [6]. These complications stand as the leading cause of both patient mortality and disability. Hence, actively investigating the underlying pathological mechanisms of DM and its associated complications is crucial in developing effective preventive strategies to mitigate and potentially reverse the detrimental effects of this condition.

The progression of the disease is greatly influenced by a combination of genetic and environmental factors [2]. Among the genetic factors, single nucleotide polymorphisms (SNPs), the most prevalent form of genetic variation among individuals within a species, are recognized as robust markers for genetic mapping and comprehensive genome-wide association analyses [7]. Vascular problems are the DM's pathological trait. Hyperglycemia chronicity is associated with long-term damage and deterioration of multiple organ systems [3].

DM and unsuccessful glycaemic management are hazardous factors for DM complications, and the predisposition to such comorbidities is expanded by ethnic variability in the genotype of the individual [8]. T2DM is a multifactorial disease, with its etiology affected by multiple genes (i.e., polygenic) and environmental factors. Indeed, genome-wide association studies (GWASs) have linked aberrations in more than 40 genes with an increased risk of T2DM. These genes are involved in the regulation of various biological processes, including cellular development, differentiation, and physiological functions. Environmental factors associated with an increased risk of T2DM include age, obesity, and lack of physical activity [9].

The persistent hyperglycemia in DM can ultimately lead to adverse complications, such as neuropathy, retinopathy, nephropathy, and cardiovascular diseases (CVDs). As a compounding factor, there is a prolonged pre-detection period in T2DM, during which one-third to one-half of all patients may go undiagnosed due to a lack of clinical symptoms. Indeed, some patients are only diagnosed with T2DM after the manifestation of complications associated with T2DM-induced hyperglycemia [9].

In the expansion of DM vascular problems, growth factors are assumed to play a decisive role [10]. It was revealed that insulin-like growth factor-1 (IGF-1) can be connected to complications of delayed microvascular DM, comprising diabetic nephropathy [7]. The IGF-1 gene is placed on chromosome 12q22-24.1, and the encoded IGF-1 protein exists as a single-chain polypeptide comprising seventy amino acids [10]. The IGF-1 and its particular receptor (insulin-like growth factor 1 receptor), adding to their mitogenic influences, profoundly impact the metabolism of protein and glucose [11].

Zinc is widely spread. It is a substantial part of about 10 percent of human proteins and is like a key in cell signaling. In humans, it exists in elevated levels in the pancreatic beta cells, where it plays an eloquent function in insulin and glucagon secretion [12]. The response to elevated levels of glucose primarily prompts the release of insulin. However, it's important to acknowledge that other factors, apart from glucose, also contribute to insulin release, such as amino acids, fatty acids, and various hormones [13]. When circulating glucose levels rise, β-cells primarily intake glucose through the glucose transporter 2 (GLUT2), which acts as a glucose sensor for these cells. Once glucose enters, it initiates glucose breakdown, thereby increasing the ratio of ATP/ADP within the cell. This ATP/ADP ratio rise prompts the closure of ATP-dependent potassium channels in the cell's outer membrane. Consequently, the membrane depolarizes and triggers the opening of voltage-dependent calcium (Ca^{2+}) channels, allowing Ca^{2+} influx into the cell. The heightened concentration of intracellular Ca^{2+} then stimulates the preparation and fusion of insulin-containing granules with the cell's outer membrane, leading to insulin release through exocytosis [14, 15]. Zinc equilibrium abnormalities have been displayed to be shared in multiple non-communicable diseases, like T2DM, age-mediated macular degradation, and liver disorders associated with alcohol [16].

In conclusion, exploring the correlation between single nucleotide polymorphisms in the IGF-1 gene

and T2DM remains an active study area within the genetics and diabetes research domain. Comprehending the genetic factors involved in T2DM may pave the way for personalized treatments or interventions for at-risk individuals, potentially enabling more precise strategies for preventing and managing this widespread metabolic disorder. So, since diabetes causes a serious threat to human health due to its complications, this study aimed to assess the association of IGF-1 gene single nucleotide polymorphism with T2DM.

Materials and Methods

This case-control study was conducted in Merjan Hospital in Babylon Province, Iraq, in 2022. Two groups of healthy individuals (n=50 as control) and T2DM patients (n=158 as study) were selected by the available random sampling method by specialist physicians. All samples signed the consent form to participate in the study.

Specimens of venous blood were withdrawn from each participant posterior to overnight fasting via plastic syringes in the seated posture. The serum levels of glucose and zinc were determined by spectrophotometric method. The serum IGF-1 level was estimated using the sandwich ELISA technique.

The DNA was extracted from blood [12], and genotyping of rs10860860 polymorphism of the *IGF-1* gene was done via polymerase chain reaction (PCR). The PCR was used for amplification of DNA by using particular primers (Forward primer: 5'-AGGACCTGGCAAATGATG-3'; Reverse primer: 5'-TATGGCAATTACATATTGGAATG-3') [13].

The thermal cycler was utilized to determine the SNP (initial denaturation for 5 minutes at 94°C, followed by 35 cycles under denaturation for 30 seconds at 94°C, annealing for 30 seconds at 60°C, elongation for 30 seconds at 72°C and then final elongation for 5 minutes at 72°C).

The products of PCR were analyzed on 2% agarose gel by electrophoresis. The PCR product fragment was 417bp. After the digestion of the PCR product by the restriction enzyme (FauND I) and following the analysis of the digestion restricts by electrophoresis, there were three possible forms of genotype for each DNA sample; the fragment with 417bp indicated the existence of the genotype TT, the fragments with 272bp and 145bp pointed to the existence of the genotype AA, the fragments 417bp, 272bp and 145bp pointed out the presence of the genotype AT.

The students' T and Chi-square tests were used to assess data at a 0.05 significance level in SPSS 21 software.

Findings

The mean age of the control group was 26.72±9.50 years, and the study group was 54.61±13.53 years ($p<0.05$). The number of males was 28 (56%) in the control and 90 (56.9%) in the study group. The mean of T2DM duration was 10.49±6.99 years.

The different levels of glucose, zinc, and IGF-1 were significant between the two groups (Table 1).

Table 1. Comparing the biochemical parameters mean between the two groups (all significant at $p<0.05$ by student T-test)

Parameters	Control	Study
Glucose (mmol/L)	4.49±0.46	8.81±1.97
Zinc (mol/L)	15.11±2.20	9.53±2.09
IGF-1 (pg/mL)	478.50±402.68	365.33±288.43

Genotyping frequencies of the IGF-1 gene deviated from Hardy Weinberg equilibrium in the control group ($\chi^2=9.158$; $p=0.002$) while were consistent in the study group ($\chi^2=2.482$; $p=0.115$). The AT genotype was associated with lower odds of T2DM than those of the wild genotype AA. The TT genotype was not significantly different in the control and T2DM groups. The minor allele T was non-significantly different in T2DM patients compared to the control group (Table 2).

Table 2. Frequencies and distributions of genotypes and alleles of *IGF-1* rs10860860 SNP in the two group

Parameter	Control	Study	OR	CI 95%	p-Value
Genotypes					
AA	11 (22)	64 (40.5)	Reference		
AT	35 (70)	80 (50.6)	0.392	0.185-0.834	0.015
TT	4 (8)	14 (8.9)	0.601	0.166-2.168	0.437
Alleles					
A	57 (57)	208 (66)	Reference		
T	43 (43)	108 (34)	0.688	0.434-1.089	0.110

Discussion

Even though hyperglycemia is a feature of all kinds of DM, several differences in the pathogenic processes give rise to hyperglycemia [17]. This study investigated the association of IGF-1 gene single nucleotide polymorphism (SNP) with T2DM.

The findings of this study showed a significant increase in glucose levels in the control group (healthy subjects) than in T2DM subjects ($p<0.001$). In this regard, Blonde *et al.* [18] found that many people with T2DM are not achieving good glycemic control, indicating that their glucose levels are higher than normal.

In the pancreas, beta cells own the greatest zinc levels, and 70 percent of the overall zinc amount is present with insulin secretory granules. Zinc influences insulin liberation. Thus, zinc is fundamental for the natural pancreatic task [12], and its lack is related to insulin resistance [19]. Zinc has a necessary work in regulation and in forming active and stored insulin forms. It may be answerable for the conformational changes that permit insulin to join to its receptors. It has been submitted that zinc deficiency can participate in the pathogenesis of diabetes [20]. The findings showed a significant decrease in zinc levels in the diabetic subjects than in the control group ($p<0.001$). Based on our research outcomes, Hussein *et al.* [21] observed that both

diabetic patients with and without neuropathy exhibited notably lower average levels of serum zinc compared to healthy individuals. Additionally, Farooq *et al*. [22] identified zinc deficiency in diabetic patients in contrast to individuals without diabetes, establishing a connection between inadequate glycemic control and reduced zinc levels.

Hyperzincuria and/or diminished gastrointestinal absorption might be the potential cause of hypozincemia found in diabetics [22]. This study agreed with the study of Masood N. *et al*. [23], but it disagreed with the study that was achieved by Saber *et al*. [20]. Zinc is related to growth hormone (GH) in cells, with IGF-1, and with insulin-like growth factor binding protein 3 (IGFBP-3) there is also a linkage [24]. In a systematic review and meta-analysis conducted by Jayawardena *et al*. [25] investigating the impact of zinc supplementation on Type 2 Diabetes Mellitus, the results highlighted a significant increase in insulin-like growth factor concentrations, particularly in patients with low levels of IGF-1. Nevertheless, the review noted substantial variability among the studies included. Similarly, aligning with these observations, Rocha *et al*. [26] demonstrated that supplementation with zinc led to a notable elevation in IGF-1 levels among human subjects. Concerning IGF1, zinc appears to be fundamental for IGF1 promotion of cell proliferation, stimulation of IGF1 receptor, and hepatic IGF1 gene expression [26].

About fifty percent of constitutional similarity with insulin is possessed by IGF1. The liver, kidneys, bones, and fat produce and liberate IGF1, and it is ubiquitous in a variety of tissues. It binds to specific IGF-1 receptors. It has a certain cross-role with insulin receptors. It exhibits insulin-like metabolic roles [27]. The IGF-1 elicits nearly the same hypoglycemic response of insulin. This leads to an increase in peripheral glucose uptake and decreased hepatic glucose production, causing better insulin sensitivity. The liver is where IGF-1 is largely manufactured after GH stimulation and is usually bound to IGFBP-3 in circulation [28].

The findings showed a significant decrease in the mean IGF-1 level in T2DM subjects than in the control group (p=0.03). This finding is consistent with the outcomes of Mancuso *et al*. in which lower circulating IGF-1 levels had been correlated with T2DM [29] and in accordance with Teppala *et al*. study in which dropped serum levels of IGF-1 were interrelated with DM [30]. Towering levels of insulin may indirectly raise the bioavailability of IGF-1 by putting down the generation of insulin-like growth factor binding protein-1. In turn, raised IGF-1 bioavailability can reverse feedback impact on GH, leading to a drop in GH secretion and lower liver manufacturing of IGF-1 and IGFBP-3 [31]. According to Drogan *et al*. [32], their unadjusted analyses revealed that the average levels of IGF-1 were lower in participants who eventually developed Type 2 Diabetes Mellitus compared to those in the random subcohort. However, when employing the multivariable-adjusted (basic) model, the study did not establish a significant association between serum IGF-1 concentrations and the risk of developing T2DM. The level of IGF1 decreases with age [33].

The results of this study proposed that lowering serum zinc levels might impact IGF-1 levels. Zinc deficiency was joined by decreased circulating IGF-1. It was recorded that zinc deficiency causes a reduction in serum IGF-1[34]. Thus, multiple factors affect the serum level of IGF-1. The IGF-1 level in circulation may not accurately describe IGF-1 bioactivity; hence, genetic-dependent research can be a substitute approximation [35]. The deviations from HWE may be attributed to the sample size, which is relatively small [36]; hence, a larger number of participants is requisite.

In this study, the AT genotype was associated with lower odds of T2DM than the wild genotype AA; this outcome meant a negative association with the disease; hence, AT was not a risk factor or might be significantly protective against T2DM. This result disagreed with the outcome of Hegazi *et al*., who found that genotype AT was not significantly different in control and DM groups [37]. In the current study, the TT genotype was found not significantly different in control and T2DM groups, which is consistent with the outcome of Hegazi *et al.* [37]. The minor allele T was non-significantly different in patients compared to the control group. While various studies propose a potential link between the minor allele T and an elevated risk of Type 2 Diabetes Mellitus and its associated complications, along with a potential decrease in mean IGF-1 levels in individuals with T2DM compared to healthy individuals, the results obtained from investigations into the relationship between the minor allele T and T2DM have not been consistent. Consequently, further research is warranted to comprehensively elucidate the connection between the minor allele T and its impact on susceptibility to T2DM.

Conclusion

The AT genotype of IGF-1 gene SNP rs10860860 negatively associates with Type 2 Diabetes Mellitus.

Acknowledgments: The authors thank Al-Mustaqbal University for the support provided to accomplish this study (grant number: MUC-M-0222).

Ethical Permissions: The research was approved by the ethics committees of the Ministry of Higher Education and Scientific Research and the Iraqi Ministry of Health (approval number: DSM-FO-1794).

Conflicts of Interests: None declared by the authors.

Authors' Contribution: AbdulAemah MA (First Author), Introduction Writer/Original Researcher/Discussion Writer (50%); Hussein GM (Second Author), Methodologist/Assistant Researcher/Discussion Writer (30%); Hussein NY (Third author), Assistant Researcher/Statistical Analyst (20%)

Funding/Support: None declared by the authors.

References

1. Li XQ, Zheng X, Chen M, Zhao MH. Characteristics of diabetic nephropathy patients without diabetic retinopathy: A retrospective observational study. Med. 2017;96(18):e6805.
2- Ali Khan I, Poornima S, Jahan P, Rao P, Hasan Q. Type 2 Diabetes Mellitus and the Association of Candidate Genes in Asian Indian Population from Hyderabad, India. J Clin Diagn Res. 2015;9(11):GC01-GC05.
3. Idowu AA, Ajose AO, Adedeji AT, Adegoke AO, Jimoh KA. Microalbuminuria, other markers of nephropathy and biochemical derangements in type 2 diabetes mellitus: Relationships and determinants. Ghana Med J. 2017;51(2):56-63.
4- Liu H, Wang X, Gao H, Yang C, Xie C. Physiological and pathological characteristics of vascular endothelial injury in diabetes and the regulatory mechanism of autophagy. Fron Endocrinol. 2023;14:1191426
5- Petrie JR, Guzik TJ, Touyz RM. Diabetes, hypertension, and cardiovascular disease: clinical insights and vascular mechanisms. Can J Cardiol. 2018;34(5):575–84.
6- Ji L, Tian H, Webster KA, Li W. Neurovascular regulation in diabetic retinopathy and emerging therapies. Cell Mol Life Sci CMLS. 2021;78(16):5977–85.
7- Hsu TH, Ning Y, Gwo JC. AFLP-SSCP: A useful AFLP-based method for informative SNPs discovery in non-model organisms. Adv Biol Chem. 2014;4(6):50291
8- Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol. 2016;12(6):357–70.
9- Hasan Ahmad SA, Ansari SA, Mensah-Brown EPK, Emerald BS. The role of DNA methylation in the pathogenesis of type 2 diabetes mellitus. Clin Epigenetics. 2020;12(104)
10- Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol Pathol. 2001;54(5):311–16.
11- Varewijck A, Janssen J. Insulin and its analogues and their affinities for the IGF1 receptor. Endocr Relat Cancer. 2012;19(5):63–75.
12- Zhao T, Huang Q, Su Y, Sun W, Huang Q, Wei W. Zinc and its regulators in pancreas. Inflammopharmacology. 2019;27(3):453-64.
13- Galicia-Galicia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Scie. 2020;21(17):6275.
14- Boland BB, Rhodes CJ, Grimsby JS. The dynamic plasticity of insulin production in beta-cells. Mol Metab. 2017;6(9):958–973.
15- Rorsman P, Ashcroft FM. Pancreatic beta-cell electrical activity and insulin secretion: of mice and men. Physiol Rev. 2018;98(1):117–214.
16- Fernandez-Cao J, Warthon-Medina M, Moran VH, Arija V, Dpepking C, Majem LS, et al. Zinc intake and status and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. Nutrients. 2019;11(5):1027.
17- Shahbaz S, Katti C, Khan M, Pawar K. Evaluation of salivary total protein in insulin dependent diabetes mellitus (IDDM) patients. Int J Cur Res Rev. 2017;9(23).
18- Blonde L, Aschner P, Bailey C, Ji L, Leiter LA, Matthaei S. Gaps and barriers in the control of blood glucose in people with type 2 diabetes. Diab Vasc Dis Res. 2017;14(3):172-83.
19- Fukasawa H, Niwa H, Ishibuchi K, Kaneko M, Iwakura T, Yasuda H. The impact of serum zinc levels on abdominal fat mass in hemodialysis patients. Nutrients. 2020;12(3):656.
20- Saber LM, Youseef AM, Abdellatif MS, Abdel Wahhab KG. Assessment of some major minerals and trace elements levels in female patients with type II diabetes mellitus and their correlation with glycated hemoglobin. Middle East J Appl Sci. 2014;4(2):345-56.
21- Hussein M, Fathy A, Elkareem RA, Marzouk S, Shawki Kamal Y. Zinc deficiency correlates with severity of diabetic polyneuropathy. Brain Behav. 2021;11(10);e2349.
22- Farooq DM, Alamri AF, Alwhahabi BK, Metwally AM, Kareem KA. The status of zinc in type 2 diabetic patients and its association with glycemic control. J Family Community Med. 2020;27(1):29-36.
23- Masood N, Baloch GH, Ghori RA, Memon IA, Memon MA, Memon MS. Serum zinc and magnesium in type-2 diabetic patients. J Coll Physicians Surg Pak. 2009;19(8):483-6.
24- Adriani M, Wirjatmadi B. The effect of adding zinc to vitamin A on IGF-1, bone age and linear growth in stunted children. J Trace Elem Med Biol. 2014;28(4):431-5.
25- Jayawardena R, Ranasingha P, Galappatthy P, Malkanthi R, Constantine GR, Katulanda P. Effects of zinc supplementation on diabetes mellitus: a systematic review and meta-analysis. Diabetol Metab Syndr. 2012;4(13).
26- Rocha EDM, Brito NJN, Dantas MMG, Silva AA, Almedia MG, Brandao-Neto J. Effect of zinc supplementation on GH, IGF1, IGFBP3, OCN, and ALP in non-zinc-deficient children. J Am Coll Nutr. 2015;34(4):290-9.
27- Ren W, Zhao C, Wang Y, Fang Y, Huang Z, Chen W, et al. Ramipril can alleviate the accumulation of renal mesangial matrix in rats with diabetic nephropathy by inhibiting insulin-like growth factor-1. Acta Cir Bras. 2019;34(1):e20190010000007
28. Maximus PS. Insulin like growth factor 1 is linked to higher cardiovascular risk score in adults with type 2 diabetes mellitus and chronic kidney disease. Diabetes Metabo Syndr. 2019;13(4):2613-8.
29- Mancuso E, Mannino G, Di Fatta C, Fuoco A, Spiga R, Andreozzi F, et al. Insulin-like growth factor-1 is a negative modulator of glucagon secretion. Oncotarget. 2017;8(31):51719–32.
30. Teppala S, Shankar A. Association between serum IGF-1 and diabetes among U.S. adults. Diabetes Care. 2010;33(10):2257–9.
31. Sandhu MS, Dunger DB, Giovannucci EL. Insulin, insulin-like growth factor-I (IGF-I), IGF binding proteins, their biologic interactions, and colorectal cancer. J Natl Cancer Inst. 2001;94(13):972–80.
32- Dorgan D, Schulze MB, Boeing H, Pischon T. Insulin-like growth factor 1 and insulin-like growth factor–binding protein 3 in relation to the risk of type 2 diabetes mellitus: results from the EPIC–Potsdam Study. Am J Epidemiol. 2016;183(6):553-60.
33- Janssen J. IGF-I and the endocrinology of aging. Curr Opin Endocr. 2019;5:1-6.
34- Dorup I, Flyvbjerg A, Everts ME, Clausen T. Role of insulin-like growth factor-1 and growth hormone in growth inhibition induced by magnesium and zinc deficiencies. Br J Nutr. 1991;66(3):505-21.
35. Rietveld I. An insulin-like growth factor-I gene polymorphism modifies the risk of microalbuminuria in subjects with abnormal glucose tolerance. Eur J Endocrinol. 2006;154(5):715–21.
36- Elias Z. Impact of Hardy Weinberg equilibrium deviation on allele-based risk effect of genetic association studies and meta-analyses. Eur J Epidemiol. 2010;25(8):553-60.

37- Hegazi MAM, Seleem A, El-Adawy EH, Elhussini MEA. Association of IGF-I gene polymorphism with diabetic nephropathy in Egyptians with type 2 diabetes. Egypt J Intern Med. 2018;30(4):191-6.