Increase Fibroblast Activation Protein-α, but not Lowering of FGF Receptor and/or Co-Receptor, Causes Increase in Fibroblast Growth Factor-21 in T2D Independent on Diabetes Duration

Original Article

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ABSTRACT

Background: Diabetes mellitus is a major global public health issue. T2DM patients are associated with increased Fibroblast growth Factor 21 (FGF21). The reason of FGF-21 increase is controversial issue.

Aim of the Study: We aimed to investigate i) whether the increase in FGF21can explain by an increase in fibroblast activation protein-α (FAP-α) rather than inhibition in fibroblast growth factor receptor 1c (FGFR1 c) and/or β-Klotho (KLB). ii) The impact of DM duration on fibroblast growth factor 21 (FGF21), FGFR1c, KLB, and FAP-α. Subject and Methods: A total of forty participants were enrolled in this study. They were divided into: 20 healthy participants, and T2D groups which were included 9 participants (recently diagnosed as T2D) and 11 participants (were T2D with diabetes duration 1-6 years). Biochemical investigations (HbA1c, glucose level, lipid profile) and FGF21, FGFR1 c, KLB and FAP-α were measured in all participants.

Results: Our results showed that FGF-21 increased significantly by 2 folds in T2D (186.7±9.8 vs. 86±2.8, respectively), the level of FAP-α was also increased significantly in T2D group without effecting the KLB level, however, there was a slightly significant increase in FGFR1c. Moreover, prolong DM duration had no effect on the FGF21 and its receptor and co-receptor. Although, FAP-α was not affected by DM duration.

Conclusion: We conclude that FGF-21 resistance could be explained by deactivation of FGF-21 by FAP-α and the DM duration had no effect on FGF-21 and FAP-α or receptor and co-receptor.

Key Words: FGF-21, FGFR1c, FAP-α, KLB, T2D.

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INTRODUCTION

Diabetes mellitus has become a major global public health issue, with a notable rise in its prevalence in recent years. The number of T2D people assumed to increase to 629 million by 2045[1,2].

Fibroblast growth Factor-21 (FGF-21) an endocrine hormone that secrets from the liver, and has an important role in regulation of glucose and lipid metabolism[3]. The FGF-21 belongs to FGF superfamily, which consists of 22 members. These members need to bind to the receptors (FGFR1c) via their heparin binding domain, this domain is lacked in three members of FGF superfamily (FGF-19; FGF-21; and FGF-23). The later three FGFs have a critical role in metabolism and to exert their endocrine functions they need to bind to the FGFR1c and because they lacked the binding domain, therefore, they need to the unique-transmembrane co-receptor α- or β-Klotho (KLB)[4-7]. Achieving the function of FGF21 is linked to present of KLB on a target tissues. KLB is presented on the liver and white adipose tissue[8, 9]. In animal studies, exogenous FGF-21 improves insulin resistance, body weight, hyperglycemia, and hepatic steatosis[10-12]. In human, the level of FGF-21 is increased in fasting state,

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however, prolong fasting is associated with decline in the FGF-21 level[13]. Furthermore, the level of FGF-21 has been shown to increase with insulin resistance[14], obesity, metabolic dysfunction-associated steatotic liver disease (MASLD)[15], and Type 2 diabetes (T2D)[6, 7, 16]. Although, a specific FGF-21 analogue improves lipid profile by lowering triglycerides (TG) and Low-density lipoprotein (LDL) and increasing the level of High-density lipoprotein (HDL)[17-19]. This increase in the FGF-21 level in metabolic disorder was explained by FGF-21 resistance[20-22] and this resistance is mostly due to FGFR1c and KLB suppression[23]. Moreover, a transmembrane serine protease, Fibroblast activation protein-α a member of the prolyl peptidases proteolytic enzyme has been identified as inactivator of FGF-21 via cleavage the C-terminal of FGF-21 on proline 171. Ten amino acids are cleavage and diminished the binding to the co-receptor (KLB)[24, 25] and this could be another hypothesis to explain the FGF-21 resistance[24, 26].

AIM OF THE WORK

Our aims were to investigate i) whether the increase in FGF21could be explain by increase in FAP-α rather than inhibition in FGFR1 c and/or KLB. ii) The impact of DM duration on FGF21, FGFR1c, KLB, and FAP-α.

PATIENTS AND METHODS

A total of forty participants were enrolled in this study. They were divided into: 20 healthy participants; 9 participants were recently diagnosed as T2D; and 11 participants were T2D with diabetes duration 1-6 years. All type 2 diabetic participants had no treatment for hyperglycemia and hyperlipidemia. A five ml fasting (14 h) venous blood were withdrawn, 1 ml was kept in EDTA tube for HbA1c measurement, and the rest 4 ml were kept in gel tube for biochemical and hormonal investigations. Fasting plasma glucose and lipid profile were measured by enzymatic colorimetric[27, 28]. HbA1c was measured by a ratio of concentrations of HbA1c to total hemoglobin using Roche c111 analyzer by immunoturbidimetric method[29].

Total FGF21(ELK Biotechnology, ELK1323, USA), FAP-α (ELK Biotechnology, ELK3985, USA) , FGFR1c (ELK Biotechnology, ELK2848, USA) and KLB (ELK Biotechnology, ELK3813, USA) levels were measured by ELISA (Sandwich enzyme immunoassay) according to the manufacturer's instructions. Microplate Reader ELISA (PARA MEDICAL) was used to measure the OD at 450 nm.

Statistical analysis:

Mean ± SEM are used to present all results in this study. GraphPad PRISM software 8.4 was used to analyze our data. One-way ANOVA was used to performed statistical difference and Sidak's multiple comparisons test was used as post-hoc test. Either students' t.test or one-way analysis of variation (ANOVA) was used for *P-value* <0.05 as indicated underneath each figure and/or table.

ETHICAL CONSIDERATION

All participants were informed and they signed the consent form before starting the study. The Ethical approve of this work was provided by the Iraqi Ministry of Health and Diwaniyah Teaching Hospital (24, 2/10/2024) the Declaration of Helsinki was followed in this project.

RESULTS

In this study, our primary objective was to test whether FGF-21 resistance could be explained be deactivation of FGF-21 by the cleavage enzyme FAP-α. The hepatokine hormone (FGF-21), its receptor and co-receptor (FGFR1c and KLB), and the cleavage enzyme (FAP-α) were measured in both T2D and healthy groups. Our participants were divided into two main groups according to their cases as shown above in patient section. There was no significant difference in age between T2D and healthy group (48.4±2.2 vs. 49.5±2, respectively). The percentage of female was higher than male in healthy and T2D (70% and 65%, respectively). As expected, the level of plasma glucose and HbA1c were increased significantly in T2D (10.6±0.75 vs. 5.6±0.2 and 8.6±0.46 vs. 5.2±0.06, respectively). Moreover, lipid profile was dysregulated in T2D group when compared with healthy group as shown in (Table 1).

Table 1: Characterizations and Biochemical markers of all participants.

	Healthy *n*=20	T2D *n*=20	*P-value*
Age	49.5±2.0	48.4±2.2	NS
Sex			
Female n (%)	14 (70%)	13 (65%)	
Male n (%)	6 (30%)	7 (35)	
fasting duration (hour)	11.9±0.35	12.4±0.32	NS
T2D duration (year)	-------	0-6	
FPG (mmol/L)	5.6±0.2	10.6±0.75 **	0.001
HbA1c (%)	5.2±0.06	8.6±0.46 **	0.001
CHO	4.1±0.14	5.4±0.24 **	0.001
TG	1.4±0.1	3.5±0.31 ***	0.0001
HDL-C	1.05±0.03	0.75±0.04 **	0.001
LDL-C	2.9±0.0.015	4.3±0.23 ***	0.0001
non-HDL	3.1±0.0.16	4.6±0.24 **	0.001
VLDL	0.17±0.01	0.4±0.03 ***	0.0001

Abbreviations: CHO Total Cholesterol; FPG fasting plasma glucose; HDL-C High-Density Lipoprotein-Cholesterol; LDL-C High-Density Lipoprotein-Cholesterol; TG Triglycerides; VLDL Very-Low Density Lipoprotein. *P<0.05; **P<0.01 vs. healthy group, NS Non-significant.

Next, we test the role of hepatokine hormone, its receptor (FGFR1c); co-receptor KLB; and the cleavage enzyme FAP-α in T2D. Our results showed that the level of FGF-21 was increased significantly (P<0.00000) by ≈ 2 folds in T2D (186.7±9.8 vs. 86±2.8, respectively) (Figure 1A). This increased in FGF-21 was concomitant with a significant elevation in the protolytical enzyme of FGF-21, FAP-α, the level was raised in T2D (0.96±0.03 vs. 0.54±0.03, respectively) (Figure 1B). These results were concomitant with a significant increase (*p-value* 0.04) in FGFR1c in T2D group (4.7±0.09 vs. 4.2±0.17, respectively), while the co-receptor, KLB, showed no change (2069±64.6 vs. 1996±59.8, respectively) (Figure 1C-D). Collectively, our results showed an increase in the FGF-21 level in T2D with concomitant increase in proteolytic enzyme with no change in KLB. This indicated that increase FGF-21 level is most likely explained by deactivation of FAP-α but not by inhibition of FGFR1c and/or KLB.

Furthermore, our second goal was to investigate the impact of DM duration on the level FGF-21; FAP-α; FGFR1c; and KLB. Therefore, T2D group was subdivided according to DM duration into recently diagnosed and 1-6 years DM duration both groups had no anti-hyperglycemic medications previously. As shown in (Table 2), the age was non-significant between recently diagnosed and 1-6 years T2D duration group (47.3±4.1 vs. 49.1±2.7, respectively). All participants in both groups were fasting for about 14h before blood sample been collected. Fasting plasma glucose showed a non-significant difference between groups. HbA1c, like plasma glucose also showed a non-significant difference.

Table 2: Characterizations and Biochemical markers of T2D patients divided according to DM duration.

	T2D <12 months *n*=9	T2D 1-6 years *n*=11	*P-value*
Age	47.3±4.1	49.1±2.7	NS
Sex			
Female n (%)	5 (56%)	8 (73%)	
Male n (%)	4 (44%)	3 (27)	
Fasting duration (hour)	13.1±0.38	12.7±0.42	NS
FPG (mmol/L)	10.5±1.5	10.6±0.75	NS
HbA1c (%)	8.7±0.77	8.6±0.6	NS

FPG fasting plasma glucose and NS non-significant.

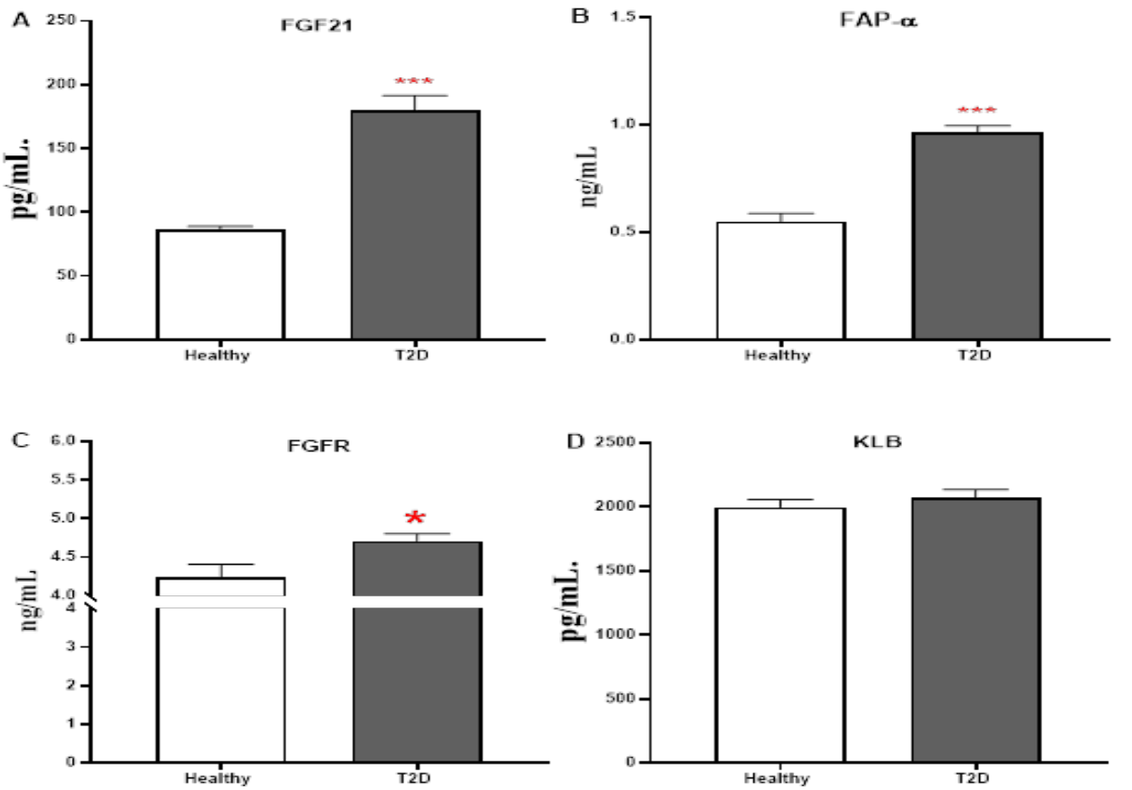

Fig. 1: T2D did not affect the co-receptor of FGF-21 unlike FGFR1c. (A) Fibroblast Growth Factor-21 (FGF-21); (B) Fibroblast activation protein-α (FAP-α); (C) Fibroblast growth Factor receptor 1c (FGFR); and (D) The Co-receptor β-Klotho (KLB). Results are presented as Mean±SEM; *n*= 20 healthy; and 20 T2D participants. **P*<0.05 relative to Healthy; ****P*<0.0001 relative to healthy. *P-value* was calculated as unpaired Student's t.test.

Later, we tested the effect of DM duration on lipid profile. Our results revealed that serum cholesterol (CHO) tend to increase but not significant in recently diagnosed group (4.9±0.36 vs. 4.1±0.14, respectively). While, CHO was more aggravate in 1-6 years DM duration (5.7±0.29 vs. 4.1±0.14, respectively) (Figure 2A). TG was increased significantly in both groups (2.82±0.35 and 3.96±0.43 vs. 1.45±0.1, respectively). Moreover, there was a significant increase in the level of TG in 1-6 years DM duration compared with recently diagnosed group (Figure 2B). This implicated the role of DM duration on TG level. HDL-C was decreased in T2D group independent on DM duration (0.76±0.08 and 0.74±0.4 vs. 1.05±0.03, respectively) (Figure 2C). LDL-C was increased in both groups (3.88±0.37 and 4.51±0.27 vs. 2.9±0.15, respectively) (Figure 2D). VLDL, similar to TG, showed a significant increase in both groups and with a significant difference between recently diagnosed and 1-6 years DM duration (0.33±0.04 and 0.46±0.05 vs. 0.17±0.01, respectively) (Figure 2E). Altogether, dyslipidemia became more pronounced in prolong DM duration.

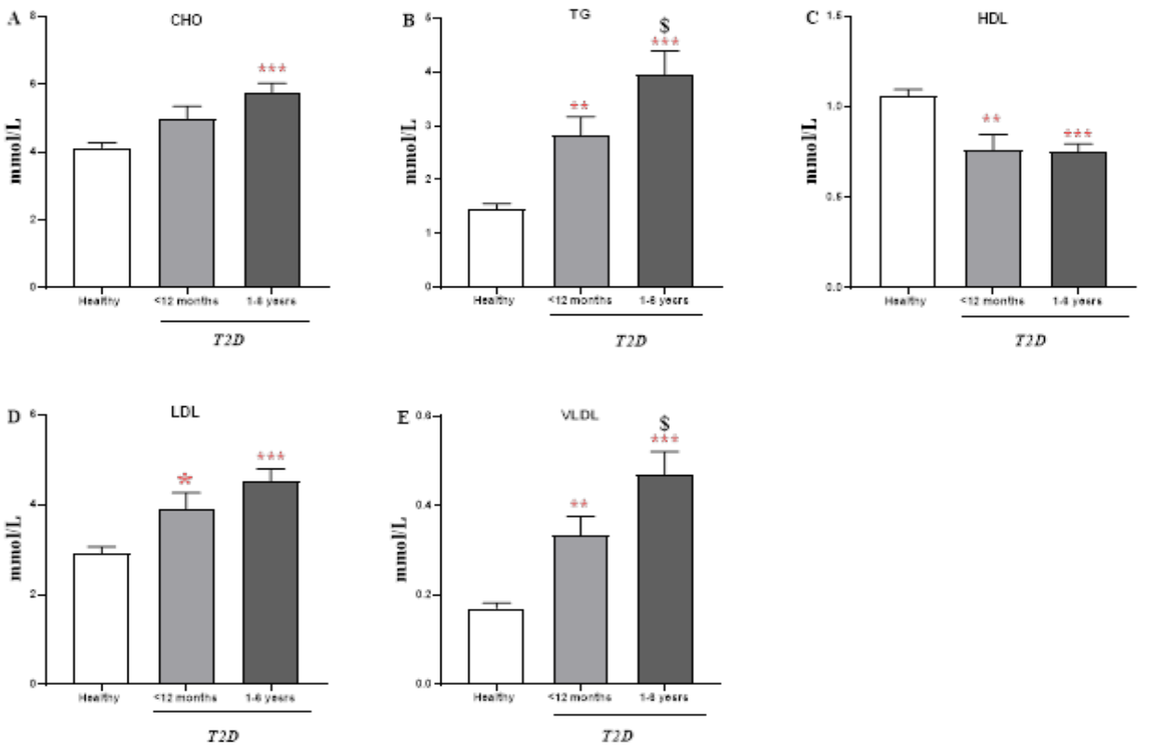

Fig. 2: Prolong DM duration causes dyslipidaemia more aggravate in T2D patients. (A) Cholesterol (CHO); (B) Triglycerides (TG); (C) High-Density Lipoprotein (HDL); (D) Low-Density Lipoprotein (LDL); and (E) Very-Low Density Lipoprotein. Results are presented as Mean±SEM; (Healthy *n*= 20); (<12 months patients diagnosed as T2D since less than 12 months; *n*=9), and (1-6 years patients diagnosed as T2D since 1-6 years; n=11). **P*<0.05; ** *P*<0.01; and *** *P*<0.001 vs. healthy. $ *P*<0.05 relative to <12 months. One-Way ANOVA (Post Hoc test; Sidak's test) was used to test *P-value*.

Moreover, the effect of DM duration on hepatokine hormone, receptor and co-receptor, and the cleavage enzyme was investigated in this study. Our results showed that FGF-21 was increased in both T2D groups compared with healthy group (178.2±23.5 and 181.2±11.6 vs. 86.0±2.8, respectively) (Figure 3A). This result was concomitant with increase in FAP-α (0.92±0.03 and 0.98±0.05 vs. 0.54±0.03, respectively) (Figure 3B), but not associated with any changes in either FGFR1C (4.7±0.17 and 4.6±0.09 vs. 4.2±0.17, respectively) (Figure 3 C) or KLB (2041±126.6 and 2088±68.9 vs. 1996±59.8, respectively) (Figure 3D). Although, there were no significant differences in all markers between <12 months group and 1-6 years group. Collectively, the above results indicated that i) increase the level of FGF-21 in T2D could be explain by increase in FAP-α but not by inhibition of FGFR1c and/or KLB; and ii) DM duration has no effect on FGF-21, receptor and co-receptor of the FGF-21 (FGFR1c and KLB); and FAP-α.

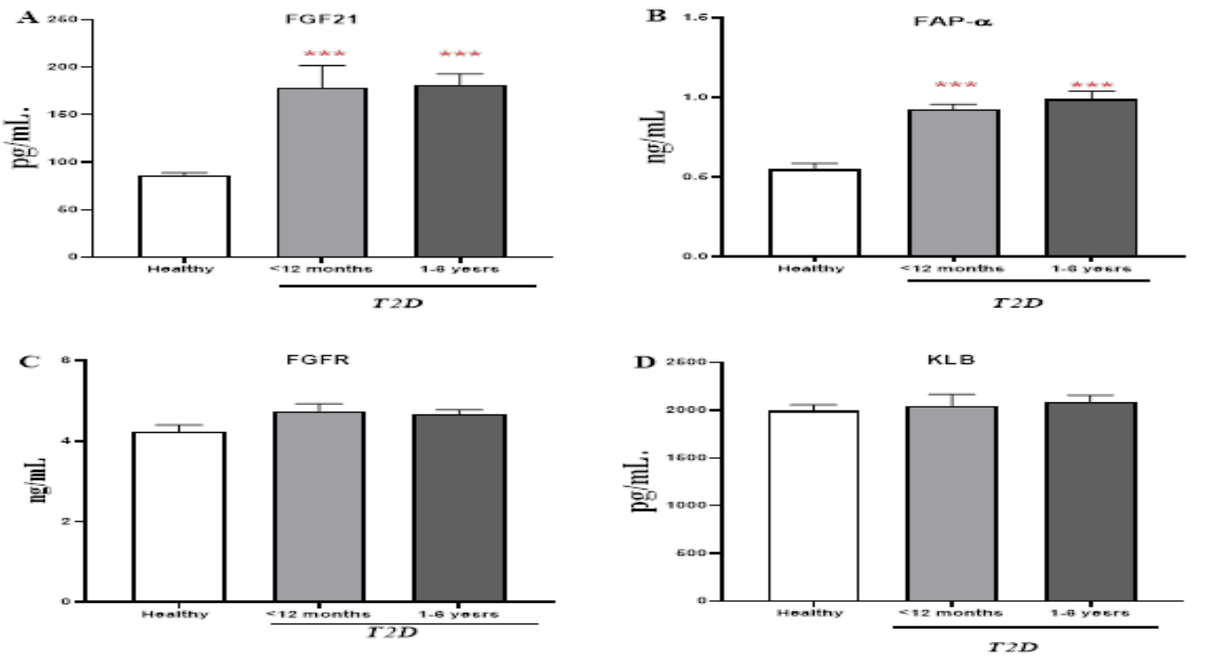

Fig. 3: FGF21 and FAP-α is increased in T2D independent on DM duration. (A) Fibroblast Growth Factor-21 (FGF-21); (B) Fibroblast activation protein-α (FAP-α); (C) Fibroblast growth Factor receptor 1c (FGFR); and (D) The Co-receptor β-Klotho (KLB). Results are presented as Mean±SEM; (Healthy *n*= 20); (<12 months patients diagnosed as T2D since less than 12 months; *n*=9), and (1-6 years patients diagnosed as T2D since 1-6 years; *n*=11). *** *P*<0.001 relative to healthy. One-Way ANOVA (Post Hoc test; Sidak's test) was used to test *P-value*.

DISCUSSION

The prevalence of T2D and its complication has been increased globally. There are too many changes associated with T2D leading to effect the glucose and lipid metabolism[30, 31]. Fibroblast growth Factor-21 has been linked with T2D. Studies showed that FGF-21 increased in the circulation of T2D[6, 7, 16]. Here, we find that FGF-21 elevation in the circulation of T2D is associated with increased in FAP-α but not with decreased in either FGFR1c or KLB, and the duration of diabetes has no effect on the level of FGF-21, FAP-α. These results will discuss carefully.

Our results showed that the increment of FGF-21 level was associated with significant increase in the cleavage enzyme FAP-α and without changes in both receptor and the co-receptor of FGF-21. Previous studies reported that the circulation level of FGF-21 is elevated in T2D[22, 32] and these results are in agreement with our finding. However, Shil et al explained the resistance of FGF-21 due to lowering of KLB in adipose tissue[22]. FGF-21 is produced by the liver and delivered into circulation. The main target tissues are the white adipose tissue and liver and achieving the activity of FGF-21 depending on FGFR1c and the co-receptor KLB. It plausible that FGF-21 resistance is explained by decrease in FGFR1c and/or KLB[8, 9, 33] however, our results did not showed any decrease in the receptor or co-receptor of the FGF-21 as shown in figure 1 A-D and prolong DM duration showed same results for an increased level of FGF-21, FAP-α in recently diagnosed and up to 6 years duration of T2D without changing in the level of FGFR and/or KLB. Therefore, the more possible explanation of FGF-21 resistance is that FGF-21 is deactivated on the binding site of FGF-21 which is allow the binding of FGF-21 to the KLB as a result of FAP-α activation[24, 25]. However, other studies linked the increase of FGF21 to inflammation and/or adipose resistance[34, 35] and our evidences cannot exclude this link.

CONCLUSION

Our findings suggest that FAP-α may play a role in FGF-21 resistance; however, further studies are needed to confirm this mechanism.

COMPETING INTERESTS

Regarding these studies, the authors have no conflicts of interest.

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AUTHORS CONTRIBUTION

Experimental designed by GHK and AA, GHK preformed the experiment, AA performed statistical analysis, GHK and AA wrote the paper.

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الزيادة في هرمون عامل النمو للخلايا الليفية-٢١ في مرضى السكري النوع الثاني هو نتيجة الزيادة في فعالية البروتين المثبط للخلايا الليفية وليس بسبب قلة مستويات المستقبل والعامل المساعد للمستقبل

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المقدمة: يعد داء السكري مشكلة صحية عامة عالمية كبرى. ارتبط مرضى السكري بزيادة عامل نمو الخلايا الليفية ٢١. ان سبب الزيادة في عامل النمو للخلايا الليفية-٢١ هو قضية مثيرة للجدل.

الهدف من الدراسة: تهدف الدراسة إلى

١)التحقيق في ما إذا كانت الزيادة في عامل النمو للخلايا الليفية-٢١ من الممكن تفسيره بالزيادة في نشاط البروتين المثبط للخلايا الليفية (FAP-α) بدلاً من التثبيط في المستقبل والعامل المساعد للمستقبل.

٢) تأثير مدة الاصابة بداء السكري النوع الثاني على هرمون عامل النمو للخلايا الليفية و البروتين المثبط للخلايا الليفية (FAP-α) ومستقبل الهرمون والعامل المساعد للمستقبل.

طرق العمل: كان هنالك أربعين مشاركا في هذه الدراسة. تم تقسيمهم إلى: ٢٠ مشاركًا أصحاء، ومجموعات ٢٠ مريض مصاب بداء السكري النوع الثاني (٩ منهم مشخصين حديثا و ١١ مشارك مصابين بداء السكري لمدة ١-٦ سنوات). تم قياس نسبة السكر الصائم و السكر التراكمي وفحص الدهون الكامل وكذلك قياس مستوى هرمون عامل النمو للخلايا الليفية-٢١, والمستقبل والعامل المساعد للمستقبل. والبروتين المثبط للخلايا الليفية لدى جميع المشاركين بالدراسة.

النتائج: أظهرت نتائجنا أن هرمون عامل النمو للخلايا الليفية-٢١ زاد بشكل ملحوظ بمقدار ضعفين في المرضى المصابين بداء السكري النوع الثاني (١٨٦,٧ ± ٩,٨ مقابل ٨٦ ± ٢,٨ على التوالي)، كما زاد مستوى البروتين المثبط للخلايا الليفية بشكل ملحوظ في مجموعة مرضى داء السكري النوع الثاني بدون التأثير على مستوى مساعد المستقبل ، ومع ذلك، كانت هناك زيادة طفيفة في مستقبل هرمون الخلايا الليفية FGFR١c. علاوة على ذلك، لم يكن لمدة الاصابة بمرض السكري النوع الثاني أي تأثير على هرمون عامل النمو للخلايا الليفية والمستقبل والعامل المساعد للمستقبل وكذلك البروتين المثبط للخلايا الليفية.

الاستنتاج: من هذه الدراسة تم استنتاج ان الزيادة في هرمون عامل النمو للخلايا الليفية-٢١ يمكن تفسيرها عن طريق تثبيط الهرمون بواسطة الزيادة في فعالية البروتين المثبط للخلايا الليفية. وان مدة الاصابة بداء السكر النوع الثاني ليس لها اي تأثير على مستوى الهرمون والمستقبل والعامل الساعد للمستقبل او البروتين المثبط.