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NOVAL IL-40 EVALUATION AND COMPARISON OF SERUM AND SALIVARY IN OBESE INDIVIDUALS WITH AND WITHOUT TYPE 2 DIABETES MELLITUS

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Abstract

Background: A robust and extensively documented association exists between Type 2 Diabetes Mellitus (T2DM) and various metabolic and inflammatory disturbances. (T2DM), obesity and persistent low-grade inflammation accompanied by disruptions in immune system function. A cytokine, Interleukin-40 (IL-40), is largely characterized by its association with B-cell activity and has garnered increasing interest due to its involvement in immune regulation and various inflammatory and autoimmune processes. Nevertheless, the potential role of IL-40 in metabolic conditions, most notably type 2 diabetes mellitus (T2DM) has yet to be thoroughly investigated, and current evidence remains scarce regarding its precise significance in this domain. Aim: This study aimed to evaluate and compare serum and salivary IL-40 levels among obese individuals with T2DM, obese individuals without diabetes, and healthy controls. Methods: Ninety participants aged 35–50 years were enrolled and divided equally into three groups: (1) obese with T2DM, (2) obese without T2DM, and (3) healthy controls. Clinical and biochemical assessments included salivary flow rate (SFR), salivary pH, body mass index (BMI), random blood glucose (RBS), glycated hemoglobin (HbA1c), and IL-40 concentrations in serum and saliva, measured by ELISAResults: Across the study cohorts, a consistent escalation in IL-40 levels was detected in both serum and saliva, with the lowest levels detected in healthy controls, followed by obese individuals, and the highest in participants with T2DM. These differences were statistically significant in all pairwise comparisons ($p=0.0001$). Moreover, serum IL-40 demonstrated a strong association with metabolic disorders, as indicated by an odds ratio of 2.45 ($p=0.014$). Individuals in the T2DM group also presented with significantly reduced salivary flow and lower salivary pH values, alongside elevated BMI and HbA1c levels compared to the other groups. Conclusion: The increased concentrations of IL-40 detected in both serum and saliva of obese and diabetic individuals point toward a possible involvement of this cytokine in the inflammatory mechanisms underlying metabolic disorders. The results underscore the prospective utility of IL-40 as a diagnostic and prognostic indicator for the early detection of Type 2 Diabetes Mellitus and for monitoring obesity-associated metabolic complications.

Keywords: Interleukin-40; Type 2 Diabetes Mellitus; Obesity; Cytokines; Salivary Flow Rate; HbAIc

1 Intrudaction

As a chronic metabolic condition, type 2 diabetes mellitus (t2dm) has emerged as a major worldwide health issue due to its increasing prevalence and related complications, primarily due to its rising prevalence and the significant medical burden it imposes. As of 2017, the worldwide prevalence of t2dm was reported to be approximately 6,000 cases per 100,000 population, with projections suggesting an increase to 7,000 cases per 100,000 by projections indicate that type 2 diabetes mellitus accounts for over one million deaths each year globally, placing it among the top ten chronic diseases in terms of mortality, ranking ninth (1). Type 2 diabetes mellitus is characterized by a combination of diminished tissue responsiveness to insulin and an inadequacy in compensatory insulin production, leading to disruptions in glucose and lipid metabolism. These disruptions typically result in hyperglycemia and dyslipidemia, both of which are key risk factors for chronic complications, including cardiovascular disease and peripheral neuropathy (2,3). It is estimated that 90% to 95% of all diabetes diagnoses fall under the type 2 category. The development of t2dm involves multiple interrelated pathophysiological mechanisms, including obesity, lipotoxicity, subclinical inflammation, and intensified oxidative pressure are critical in t2dm onset (4). Hyperglycemia induces surplus ros formation, triggering intracellular lipid oxidation, which subsequently initiates intracellular lipid peroxidation, disrupts normal cellular function, and intensifies the pathological progression of diabetes (5). Obesity, especially widespread in developed countries, poses a significant public health challenge and is closely linked to persistent low-grade inflammation in white adipose tissue (6). Central adiposity, particularly in the abdominal region (android obesity), is considered a key contributor to the initiation and advancement of type 2 diabetes mellitus (t2dm) (7). Interleukin-40 (il-40) is a newly recognized cytokine that has attracted growing attention in the scientific community for its possible involvement in regulating immune responses. Despite this, its particular role in the pathophysiology of t2dm remains insufficiently understood. First described in 2017, interleukin-40 (il-40) is primarily related to the functional activity of b lymphocytes, where it contributes to immune modulation and the preservation of b-cell equilibrium. This cytokine, approximately 27 kilodaltons in molecular weight, is encoded by the cl7orf99 gene located on the seventeenth chromosome. Its expression is predominantly observed in activated b lymphocytes, fetal hepatic tissue, and bone marrow. Due to its lack of structural homology with established cytokine families, il-40 is currently categorized as an orphan cytokine. As an orphan cytokine, il-40 is structurally distinct from other known cytokine families. Experimental evidence has demonstrated that b cells derived from the spleen are capable of producing il-40 following stimulation with anti-cd40, anti-igm antibodies, or interleukin-4. Furthermore, the expression of il-40 significantly increases when b lymphocytes are stimulated by transforming growth factor-beta (tgf-β), a cytokine acknowledged for its anti-inflammatory effects (8). Beyond b cells, il-40 production has also been identified in other immune cells, including cd68+ macrophages, as well as cd4+ and cd8+ t lymphocytes. Increased

concentrations and the presence of il-40 have been observed in both the serum and salivary glands for patients diagnosed with primary sjégren's syndrome, a systemic autoimmune condition (9). Comparable elevations in serum il-40 levels have also been observed in individuals with rheumatoid arthritis (ra), suggesting a broader role for this cytokine in mediating autoimmune and inflammatory processes (10). In light of the pivotal role that inflammation plays in the onset of both obesity and type 2 diabetes mellitus (t2dm), and acknowledging the documented alterations in b-cell immune responses among individuals with obesity-related diabetes (11), there is growing interest in understanding the immunological mechanisms involved. Il-40 may represent an important, yet insufficiently studied, component of the inflammatory cascade underlying t2dm. As b-cell dysfunction has been implicated in disease progression, and considering the established elevation of il-40 in various chronic inflammatory states, it is reasonable to hypothesize its potential contribution to the pathogenesis of t2dm (12). Beyond systemic inflammation, t2dm is frequently associated with a spectrum of oral health complications that may hold both diagnostic and prognostic relevance. The underlying mechanisms contributing to these oral changes include impaired neutrophil activity, heightened collagenase function, diminished collagen synthesis, microvascular alterations, and neuropathic damage (13), all of which collectively contribute to an increased risk of oral pathology. Individuals with t2dm frequently exhibit a variety of oral complications, including xerostomia (dry mouth), dental caries—particularly affecting the roots—periapical lesions, gingivitis, periodontitis, oral candidiasis, and burning mouth syndrome, notably, glossodynia is a frequent symptom, accompanied by other oral manifestations such as changes in taste perception, the presence of geographic or fissured tongue, coated tongue, oral lichen planus (olp), and recurrent aphthous ulcers. Furthermore, individuals with t2dm often exhibit increased vulnerability to oral infections and experience delayed healing of oral wounds (14). The prevalence and intensity of these oral complications tend to correlate strongly with both the level of blood glucose and the chronicity of hyperglycemia. Therefore, such oral changes may serve as early warning signs of metabolic dysregulation and underscore the need for incorporating oral health evaluation into the holistic management of diabetic patients (15).

2 Material and methods

From december 2024 to may 2025, a case-control study was performed at al-kindy educational hospital in baghdad, iraq, lasting for a period of six months. The research sample included 90 individuals between the ages of 35 and 50, distributed equally among three categories: obese participants without a diagnosis for type two diabetes mellitus (n = 30), obese individuals diagnosed with t2dm (n = 30), and healthy individuals who served as the control group (n = 30). The inclusion criteria encompassed individuals classified as obese (bmi >30 kg/m), with a waist circumference surpassing 80 cm in females or 94 cm in males. Additional criteria included hbaic values below 5.7% for non-diabetic participants and above 6.7% for those with diabetes, fasting blood glucose levels under 100 mg/dl for controls and 126 mg/dl or higher for diabetic individuals, of the age range between 35-50 years,

and the absence of systemic immune-related diseases. Exclusion criteria involved individuals with type 1 diabetes mellitus, prediabetes (hbaic between 5.7-6.6%), those categorized as overweight (bmi 25-30), as well as individuals with cardiovascular or rheumatic diseases, pregnant women, smokers, alcohol consumers, and those undergoing insulin therapy.

Body mass index (bmi)

Serving as a widely accepted measure of adiposity, body mass index (bmi) is computed by taking an individual's weight (in kilograms) and dividing it by the square of their height (in meters). This relationship is expressed in the following equation (16):

Bmi = mas /height (m7)

Saliva collection

Unstimulated saliva was obtained from each participant during the morning hours (between 9:00 and 11:00 am), following a thorough rinse of the mouth using sterile water. Approximately 5 ml of saliva was obtained using the passive drooling (spitting) method and transferred into sterile collection tubes. Following collection, centrifugation of the saliva samples was performed at 3000 rpm for five minutes, allowing for the clear separation of the supernatant, which was then reserved for subsequent biochemical analysis. The resulting supernatants were carefully separated and preserved at -20°c for subsequent analytical procedures (17).

Salivary ph and salivary flow rate (sfr)

Salivary ph was determined with a calibrated digital ph meter. The probe was rinsed with deionized water between measurements and fully immersed in each sample until a stable reading was achieved. Salivary flow rate was calculated for each participant by dividing the total volume of unstimulated saliva collected (ml) by the collection duration (minutes), which was precisely monitored using a digital timer. Quantitatively, salivary secretion measurements were recorded as ml/min.

Flow rate (ml/min) = saliva volume + collection time (min)

Blood collection

For each participant, a 5 ml venous blood specimen was collected into gel-based separator tubes. Following a 10 to 30-minute resting period to facilitate clot formation, the tubes underwent centrifugation at 3000 revolutions per minute (rpm) for twenty minutes. The isolated serum underwent aliquoting and was subsequently stored at -20°c for further assessment of il-40 concentrations and random blood glucose (rbs) levels. An additional 2 ml of blood was collected and analysed for hba1c.

Il-40 quantification via elisa

Interleukin-40 (il-40) concentrations in both serum and saliva samples were quantified using a commercially available human il-40 elisa kit (biotech, usa). A (sandwich elisa) approach was utilized to carry out the immunoassay analysis.

Statistical analysis

Statistical analysis was carried out with spss version 26 in conjunction with microsoft excel 2019. Data distribution was assessed and confirmed to be parametric; consequently, the results mean + standard deviation (sd) was used to

present the data. One-way anova was applied to assess differences among the study groups, while the chi-square test was performed to investigate relationships between categorical variables. To determine linear relationships between continuous variables, pearson's correlation coefficient was used. A p-value under 0.05 indicated statistical significance.

3 Results

The distribution of sex among the study groups—control, obese, and diabetes mellitus— showed that females constituted a slightly higher proportion of the total sample (57.8%) compared to males (42.2%). Specifically, females were more frequent in the obese group (21 out of 30; 40.4%) and the control group (18 out of 30; 34.6%), whereas males were more prevalent in the diabetes mellitus group (17 out of 30; 44.7%). However, the comparison of gender distribution across the groups using the chi-square test yielded a *p*-value of 0.107, demonstrating no statistically significant differences. In terms of age, the mean + standard deviation was 40.93 + 5.29 years for the control group, 42.20 + 5.50 years for the obese group, and 43.10 + 4.97 years for the group with diabetes mellitus. All study participants were between 35 and 50 years of age. The statistical evaluation revealed no meaningful variation in the average age across the three study groups (p = 0.281), as outlined in table 1.

As illustrated in table 2, the distribution of salivary ph values—categorized as acidic or alkaline—varied significantly among the three study groups. In the control group, an equal number of participants exhibited acidic and alkaline saliva, with 15 individuals in each category (32.6% and 34.1%, respectively). In contrast, the obese group demonstrated a higher frequency of alkaline saliva (21 participants; 47.7%) compared to acidic saliva (9 participants; 19.6%). Notably, the diabetes mellitus group had the highest proportion of participants with acidic saliva, accounting for 22 individuals (47.8%), while only 8 participants (18.2%) had alkaline ph levels. A statistically significant overall difference was observed among the groups (p=0.004).

Figure 1 illustrates the salivary flow rate (sfr), bmi, rbs, and hba1c levels across the control, obese, and diabetes mellitus groups. Participants with type 2 diabetes mellitus exhibited a significantly lower salivary flow rate (0.18 + 0.04 ml/min) compared to both the control group (0.31 + 0.03 ml/min) and the obese group (0.32 + 0.05 ml/min), with the difference being highly significant (p = 0.0001). Similarly, the body mass index (bmi) differed substantially across the three groups, with mean values of 24.54 + 2.34 for controls, 37.54 + 4.62 for obese individuals, and 32.02 + 3.57 for diabetic participants (p = 0.000). In terms of random blood sugar (rbs), the highest levels were recorded in the diabetic group (224.0 + 61.4 mg/dl), followed by the obese (97.6 + 10.5 mg/dl) and control groups (86.3 + 7.7 mg/dl). However, the variation observed between the control and obese groups was not statistically significant (p = 0.232). Glycated hemoglobin (hba1c) was also markedly elevated in the diabetes group (8.33 + 1.08%) relative to both the control (4.61 + 0.39%) and obese groups (4.95 + 0.37%), although the variation between the latter two was not statistically significant (p = 0.062).

Table 3 illustrates a notable and statistically significant elevation in salivary il-40 levels among the investigated groups. The control group recorded a mean concentration of 0.29 + 0.04 pg/ml, whereas the obese group demonstrated a higher average of 0.66 + 0.08 pg/ml. The highest levels were observed in the diabetes mellitus group, reaching 0.78 + 0.14 pg/ml. A significant statistical variation was detected across the study groups (p =0.0001). Subsequent analysis employing the least significant difference (lsd) post hoc test verified substantial differences across all pairwise comparisons, specifically control versus obese, control versus diabetes mellitus, and obese versus diabetes mellitus—as depicted in figure 2

Serum il-40 levels differed significantly among the study groups, as presented in table 3-22. The control group exhibited the lowest mean concentration at 0.33 + 0.05 pg/ml, in contrast, the obese group showed a considerably elevated level of 0.75 + 0.11 pg/ml. The diabetes mellitus group showed the highest mean serum il-40 concentration, measuring 1.06 + 0.17 pg/ml. Significant disparities in il-40 levels among the study cohorts were observed via one-way anova (p=0.0001), as detailed in table 4. The post hoc analysis using the least significant difference (lsd) method demonstrated statistically significant differences across all group comparisons. All pairwise group comparisons, including control vs. Obese, control vs. Diabetes mellitus, and obese vs. Diabetes mellitus (p = 0.000).

To examine the relationship between specific interleukins and metabolic conditions for conditions like obesity and type 2 diabetes mellitus, odds ratios (ors), accompanied by 95% confidence intervals (cis) and their corresponding p-values, were calculated. Median expression levels served as thresholds for analysis, as presented in table 5. Notably, serum il-40 exhibited a statistically significant association with metabolic disease, with an or of 2.45 (95% ci: 1.20-5.01; p = 0.014).

4 Discussion

The current study demonstrated notable differences in salivary ph among individuals in the control, obese, and type 2 diabetes mellitus (t2dm) groups. A higher percentage of participants within the tz2dm group (47.8%) exhibited acidic salivary ph values compared to the control group (32.6%). Conversely, participants in the obese group showed a greater prevalence of alkaline saliva (47.7%) as compared with the control group (34.1%) and our findings corroborate those reported by previous, who reported alterations in salivary characteristics, including ph, among obese individuals, potentially affecting oral health (18,19). The current study also demonstrated a significant decrease in salivary flow rate (sfr) among participants with t2dm when compared to both the obese and control groups. The mean sfr in the t2dm group exhibited 0.18 + 0.04 ml/min, which was notably lower than the values observed in the control (0.31+0.03ml/min) and obese (0.32 + 0.05 ml/min) groups. This result corroborates the observations described by (20), who noted that although obesity may influence the biochemical composition of saliva, its effect on unstimulated salivary flow rate tends to be minimal (21). Furthermore, chavez et al. (2001) reported that elderly individuals with poorly controlled diabetes often experience a diminished salivary secretion compared to individuals with optimally regulated diabetes or healthy non-diabetic subjects, despite not always

presenting subjective complaints of dry mouth (22). The current study revealed a significant difference in body mass index (bmi) across the three participant groups, indicating distinct anthropometric profiles among controls, obese individuals, and those with type 2 diabetes mellitus. The control group exhibited bmi values within the normal range, the obese group recorded the highest bmi levels, while the diabetes mellitus group showed moderately elevated bmi values. These observations align with the study by bennasar-veny et al. (2020), which reported significantly increased bmi in both pre-diabetic and t2dm individuals compared to healthy controls (23). The central deposition of adipose tissue has been commonly understood to play a crucial role in the progression of insulin resistance. Engin (2017) described obesity as a major factor in metabolic dysfunction, largely attributable to the recruitment and activation of immune cells, including macrophages, in adipose tissue. This process promotes chronic low-grade inflammation, often referred to as metaflammation, which disrupts insulin signaling pathways (24).

Conversely, research carried out by al-hasnawi et al. (2015) on an iraqi cohort did not identify a significant statistical association between body mass index (bmi) and the occurrence of type two diabetes mellitus (t2dm), indicating that such correlations may differ across populations or be influenced by other confounding variables (25).

The present study identified a distinct and statistically significant progressive increase in il-40 levels within both saliva and serum samples across the control, obese, and type 2 diabetes mellitus groups. The lowest concentrations were observed in healthy participants, while elevated levels were recorded in obese individuals, and the highest values were detected in diabetic patients. All pairwise comparisons revealed highly significant differences, underscoring the potential relevance of il-40 in metabolic dysregulation. Notably, serum il-40 exhibited a strong association with metabolic disease, reflected by an odds ratio of 2.45, and both salivary and serum il-40 demonstrated strong discriminatory capacity for diabetes mellitus in roc analysis.

Il-40 has been implicated in supporting b-cell differentiation and promoting their survival—mechanisms that may facilitate autoantibody generation and sustain chronic inflammatory states commonly observed in metabolic conditions, for instance, obesity and type two of diabetes mellitus (26). This is consistent with findings by nussrat and ad'hiah (2023), who reported higher serum il-40 levels among t2dm patients in comparison to healthy controls. More generally, cytokines are defined as low molecular weight proteins produced by diverse cell populations, functioning as key mediators in immune and inflammatory processes, and they serve essential functions in orchestrating immune responses and mediating inflammation (27). Nussrat and ad'hiah (2023) further proposed that the development and progression of t2dm may involve a complex interaction between pro-inflammatory and anti-inflammatory cytokines (28). According to catalan-dibene (2018), increased il-40 expression may enhance the release of additional pro-inflammatory cytokines, potentially establishing a feedback loop that intensifies tissue inflammation and promotes insulin resistance (29). Il-40 may also contribute to localized inflammation in adipose tissue and vascular endothelium, thereby

facilitating metabolic complications and vascular injury in diabetic patients (27). While current research linking il-40 to t2dm, obesity, or broader metabolic dysfunction remains limited, emerging evidence supports a possible role for this cytokine in chronic inflammatory processes. A previous study by navratilova et al. (2021) investigated the association between interleukin-40 (il-40) and chronic inflammatory diseases, specifically rheumatoid arthritis (ra) (28). The researchers reported statistically significant elevations in il-40 levels among ra patients, which decreased following treatment. These findings suggest that il-40 may contribute to inflammation and tissue damage in chronic disease settings. Building upon previous research, the current study proposes a possible involvement of il-40 in the immunologically mediated destruction of pancreatic beta-cells, the cellular units primarily tasked with insulin secretion in diabetic individuals. This assumption is reinforced by the findings of navratilova et al. (2021), who observed increased il-40 concentrations in individuals with rheumatoid arthritis, with a notable reduction following therapeutic b-cell depletion (30).

5 Conclusion

The findings of the current study revealed a substantial elevation in il-40 levels in both serum and saliva among obese individuals, with the most pronounced increases observed in participants with type 2 diabetes mellitus (t2dm). These data demonstrate that il-40 could play a pivotal role in the chronic inflammatory mechanisms typical of metabolic disorders.

ТАБЛИЦЫ

Table 1. Demographic data of Sex and age among study groups

		Study groups			Total	*p-value*
		Control	Obese group	Diabetes mellitus group		
Sex	Male	12 (31.6%)	9 (23.7%)	17 (44.7%)	38 (42.2%)	0.107 [a] NS
	Female	18 (34.6%)	21 (40.4%)	13 (25.0%)	52 (57.8%)	
Total		30 (33.3%)	30 (33.3%)	30 (33.3%)	90 (100.0%)	
Age	Mean ±SD	40.93±5.285	42.20±5.499	43.10±4.971	42.08±5.273	0.281 [b] NS
	Range	35-50	35-50	35-50	35-50	

Notes: [a] Chi-Square Tests, [b] ANOVA test, NS: non-significant

Table 2. pH in all groups

		Groups			Total	*p-value*
		control	Obese group	Diabetes mellitus group		
pH	acidic	15 (32.6%)	9 (19.6%)	22 (47.8%)	46 (51.1%)	0.004
	alkaline	15 (34.1%)	21 (47.7%)	8 (18.2%)	44 (48.9%)	
Total		30 (33.3%)	30 (33.3%)	30 (33.3%)	90 (100.0%)	

Table 3. Level of Salivary _IL40 in all groups

Salivary _IL40				
Study groups	Mean±Std. Deviation	Std. Error of Mean	F	p-value
Control	0.29±0.04	0.01	208.569	0.0001
Obese group	0.66±0.08	0.01		
Diabetes mellitus group	0.78±0.14	0.03		

Table 4. Level of serum_IL40 in all groups

serum_IL40				
Study groups	Mean±Std. Deviation	Std. Error of Mean	F	p-value
control	0.33±0.05	0.01	287.360	0.0001
Obese group	0.75±0.11	0.02		
Diabetes mellitus group	1.06±0.17	0.03		

Table 5. Odds ratio (OR).

Biomarker	Odds Ratio (95% CI)	P-value
saliva_IL40	0.75 (0.38–1.47)	0.410
serum_IL40	2.45 (1.20–5.01)	0.014

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РИСУНКИ

Figure 1. Level of SFR,BMI, RBS and HbA1c in all groups

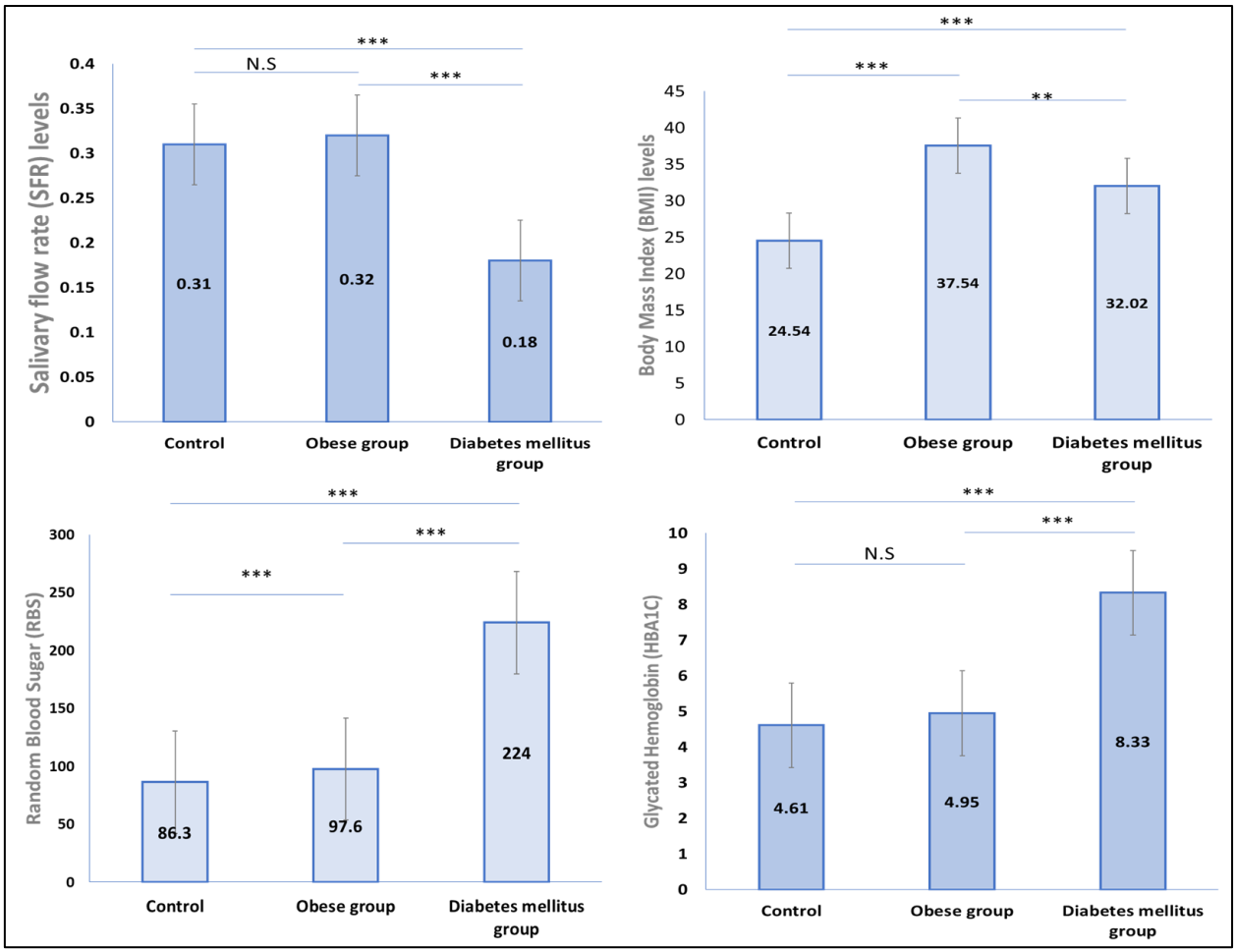

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Figure 2. Multiple Comparisons of Salivary IL40 level in all groups

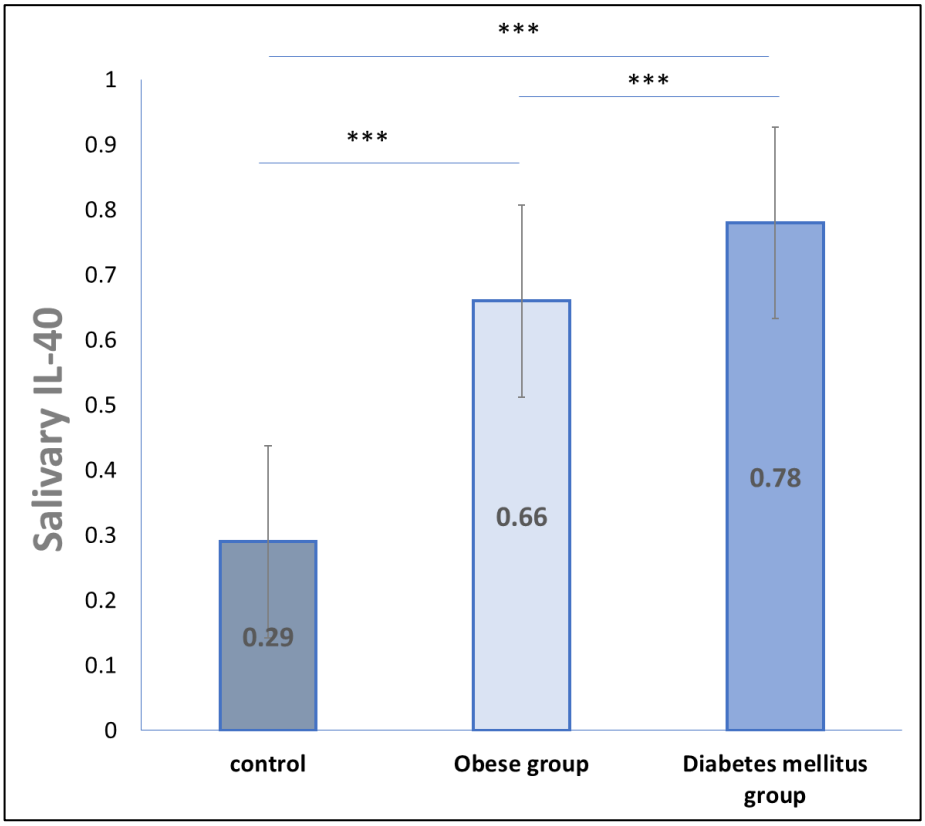

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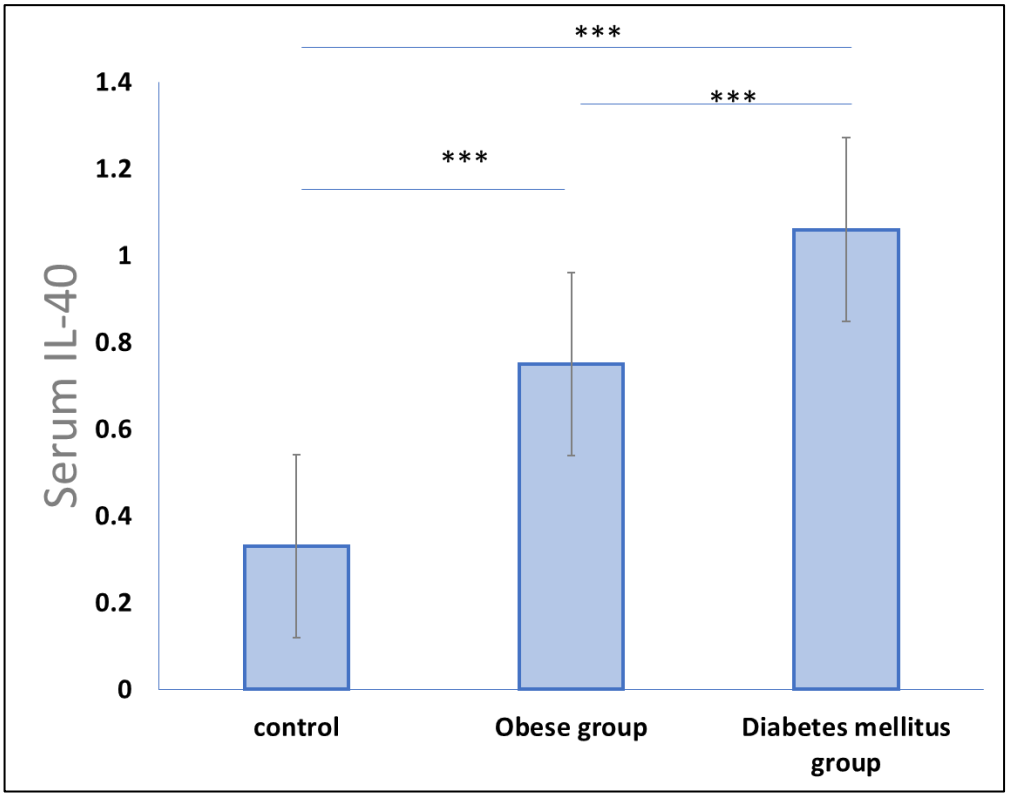
Figure 3. Multiple Comparisons of serum_IL40 level in all groups



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ТИТУЛЬНЫЙ ЛИСТ_МЕТАДАННЫЕ

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Блок 3. Метаданные статьи
NOVAL IL-40 EVALUATION AND COMPARISON OF SERUM AND SALIVARY IN OBESE INDIVIDUALS WITH AND WITHOUT TYPE 2 DIABETES MELLITUS

Сокращенное название статьи для верхнего колонтитула:

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