Immunological and Molecular Investigation of Non- *Helicobacter pylori* Gastritis within Type 2 Diabetes Mellitus

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دراسة مناعية وجزيئية لالتهاب المعدة غير الناتج عن جرثومة الملوية البوابية في مرضى السكري من النوع الثاني

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Abstract

Gastritis is one of the most common diseases in the digestive system, especially in patients with low immunity, including diabetic mellitus. Diabetic Mellitus considered one of an endocrine gland disease characterized by elevated blood sugar because of a defect in the regulation of sugar in the body. The purpose of this study was to assess the association between Non-*Helicobacter pylori* gastritis with type 2 diabetic mellitus (N-*Hp* G.T2DM), by interleukin IL-10 and IL-18. This study included 37(41.1%) N-*Hp* G.T2DM, 23 (25.6%) gastritis (G) only and 30 (33.3%) healthy participants. Biomarkers for T2DM and G (FBS, HbA1c and BMI) along with *H.pylori* IgG Ab and hs-CRP evaluated. Additionally, levels of IL-10 and IL-18 evaluated by both ELSIA and real time PCR .Through the study; we noticed a correlation between *N-Hp G.T2DM* patients and patients with G. We discovered that N-*Hp* G. T2DM associated had lower levels of Il-10 than gastritis ($p<0.0001$). In addition, that IL-18 was more highly expressed in gastritis linked to N-*Hp* G.DM than in gastritis ($p<0.0001$).

Keywords: Non-*H.pylori* gastritis, T2DM, ELISA, Real time Polymerase Chain Reaction.

المستخلص

التهاب المعدة هو أحد أكثر الأمراض شيوعاً في الجهاز الهضمي، وخاصة عند المرضى ذوي المناعة المنخفضة، بما في ذلك مرضى السكري. يعتبر مرض السكري احد امراض الغدد الصماء الذي يتميز بارتفاع سكر الدم بسبب خلل في تنظيم السكر في الجسم. كان الغرض من هذه الدراسة تقييم العلاقة بين التهاب المعدة غير الناجم عن البكتيريا الحلزونية البوابية ومرض السكري النوع الثاني بواسطة الانترليوكينات 10 و18. شملت هذه الدراسة 37 (41.1%) من مرضى التهاب المعدة غير الناتج عن جرثومة الملوية البوابية والسكري النوع الثاني (N-HP G.DM) , 23(25.6%)من مرضى التهاب المعدة فقط(G) و30 (33.3%) من المشاركين الاصحاء. تم تقييم المؤشرات الحيوية لمرض السكري من النوع الثاني والتهاب المعدة التي هي سكر الدم الصائم ,السكر التراكمي ومؤشر كتلة الجسم (FBS,HbA1C and BMI) إلى جانب تحليل جرثومة المعدة بالدم للاجسام المضادة من نوع الغلوبولين ج وتحليل البروتين المتفاعل عالي الحساسية (H.pylori IgG Ab & hs-CRP) بالإضافة إلى ذلك، تم تقييم مستويات الانترليوكينات 10 و18 بواسطة كل من الاليزا (ELIZA) وتفاعل البوليميراز المتسلسل (RT-qPCR). من خلال دراستنا لاحظنا وجود علاقة بين المرضى المصابين بالتهاب المعدة غير الناجم عن البكتريا الحلززونية والسكري النوع الثاني (N-Hp G.T2DM)مع مرضى التهاب المعدة(G). اكتشفنا أن مرضى (N-Hp G.T2DM) لديهم مستويات أقل من IL-10 مقارنة بمرضى (G) $p<0.0001$. بالإضافة إلى ذلك، تم التعبير عن IL-18 بشكل أكبر في (N-Hp G.T2DM)مقارنة ب(G) $p<0.0001$.

الكلمات المفتاحية: التهاب المعدة غير الناتج عن جرثومة الملوية البوابية, مرض السكري النوع الثاني ,اليزا, تفاعل البوليميراز المتسلسل الكمي.

1. Introduction

Gastritis term commonly used, although incorrectly to describe a range of clinical symptoms associated with upper abdomen, namely epigastrium. Although endoscopy, gastritis is characterised as presence of redness or swelling in lining of the stomach. Moreover, it is important to note that these endoscopic findings are not exclusive or limited to mucosal inflammation(Okamura *et al*., 2018). Prominent reasons for gastritis involve extended consumption of alcoholic drinks that activates caspase-1, which leads to the release of pro-inflammatory cytokines such as IL-1β and IL-18, hence triggering inflammatory pathways (Li *et al*., 2018). In addition, non-steroidal anti-inflammatory medicines (NSAIDs), such as Aspirin, used by people with Rheumatoid arthritis and Osteoarthritis. Stress, chronic bile reflux, autoimmune illnesses, and positive helicobacter pylori infection that major cause chronic gastritis. The symptoms noticed in her include nausea, vomiting, indigestion, a burning feeling, and abdominal bloating. Diagnosis often involves the blood testing, stool tests, urea breath and gastro endoscopy(Elseweidy, 2017). Gastritis is a common and typically severe condition in persons with diabetes mellitus type 2 (T2DM), likely caused by the compromised state of their immune system (Ebule *et al*., 2017). T2DM a burgeoning worldwide health issue intricately connected to the widespread prevalence of obesity. Individuals diagnosed with T2DM face a significant likelihood of developing both microvascular problems (such as retinopathy, nephropathy, and neuropathy) and microvascular complications such as cardiovascular diseases(DeFronzo *et al*., 2015). Therefore, both gastritis and T2DM affect immunity of patients including interleukins that regulation inflammatory pathways, such as interleukin 10 and 18. Anti-inflammatory

IL-10 plays an important role in regulating of immune response by down production of inflammatory cytokines in innate cells, including macrophages (MP) and dendritic cells (DCs). Immune response modulation through IL-10 demonstrated the important affect arrangement of allergy, inflammation, and autoimmune diseases (Rutz and Ouyang, 2016, Gabryšová *et al*., 2014). IL-18 considered pro-inflammatory have a crucial role in inflammatory response related to diabetes and impact on immunological responses. This interleukin involved in multiple metabolic disorder, for example type 1 and type 2 diabetes, by influencing insulin resistance and facilitating inflammation.(Chen *et al*., 2015, Zhuang *et al*., 2019). This study the investigated impact of these interleukins on N-*Hp* .T2DM by measuring concentration of these interleukins by ELIZA and their gene expression by real time polymerase chain reaction RT-qPCR.

2. Materials and methods

2.1. Specimen Collection: A total of (60) patients having dyspepsia and abdominal pain included in e study group. Every patient attended hospitals of Gastroenterology and Hepatology in Diyala and Baghdad, Iraq from January 2024 to April 2024. Total patients underwent upper gastrointestinal tract (GIT) endoscopy. Thirty healthy adult underwent standard medical examinations selected as controls. Patients with gastric cancer, type 1 diabetes, acute or chronic renal failure, cardiovascular diseases and pregnancy women excluded. The selected individuals divided into two categories: *N-Hp G* T2DM diabetic gastritis 37 and gastritis 23 (G). This classification was based on the results of gross endoscopic examination, rapid *H. pylori* urease test (RUT) and histological findings. The third group consisted of healthy individuals 30 (control). 5 ml of blood samples obtained

from all participants' then two aliquots were prepared. An aliquot of direct blood sample used to assess the RUT, FBS, and Hb1Ac. A portion of the serum utilized for the ELISA assays and kept in the freezer. For gene expression, a second aliquot put into an anticoagulant tube containing Ethylene Diamine Tetra Acetic Acid (EDTA). For gene expression research, about 250µL taken out of the EDTA tube, added Trizol reagent, and utilized. The concept and procedures of the study approved by the Ethics Committee of the Middle Technical University/ College of Medical and Health Technologies/ Baghdad. Before collecting venous blood samples, written informed consents obtained from the patients.

2.2. Biochemical assay: Detected diabetic mellitus by estimated fasting blood sugar (FBS: 70–100 mg/dl) and HbA1C values (Normal Range: less than 5.7% -6.4%).Via Cobas INTEGRA-400 plus clinical chemistry automated system. .furthermore estimate body mass index (18.5-24.9 kg/m2) for every participant

2.3. Immunological assay: via using enzyme linked immunosorbent assay (ELIZA) kit (Elabscience, USA) to calculate the levels of *H. pylori* IgG Ab by indirect ELIZA and concentration of hs-CRP, interleukin 10 and 18 by sandwich ELIZA. According to the instructions of the kit manufacturer. The concentration of all tests calculate from read absorption by Human Read HS (company human, Germany). All biochemical and immunological assay applied for all participants.

2.4. Molecular assay: gene expression of interleukin 10 and 18 gene for 7 samples from N-*Hp* G.T2DM group, 13 from G group and 13 healthy control. First step extraction total RNA from blood sample that kept with Trizol, this process according to manufacture of kit TransZol up plus RNA Kit (Transgen, China). After that examination purity and concentration of RNA via Nano drop for all samples ranged (1.90-2.02). Second, convert RNA to

cDNA (reverse transcription RNA), by utilising the Easy Script® One Step gDNA Removal and cDNA Synthesis Super Mix Kit from (Transgen, China). finally step including using the cDNA products, real-time PCR carried out after reverse transcription-PCR. Using a SYBR Green PCR two- cycling employed, comprising denaturation at 94°C for 10 sec , annealing at 64°C for 15 sec and extension step at 72 °C for 20sec. The reaction mixture comprised 10µl of SYBR Green PCR Master Mix, 2µl of primers, 2µl of template DNA or cDNA, and 6µl of RNase-free water. The parameters for real-time PCR were as follows: 30 sec of initial denaturation at 94°C, followed by 45 cycles of 10 seconds at 94°C and 15 seconds of annealing at 64°C. The expression of each gene was analysed relative to that of GAPDH. The genes encoding IL-10 and IL-18 evaluated. The primer and probe sequences utilised in this real-time PCR enumerated in Table (1). The 2-ΔΔCT method enables the use of real-time quantitative PCR to examine relative alterations in gene expression.

Table (1): Real time PCR Primers sequence for IL-10 and 1L-18 Gene

Gene	Primer Sequence 5`-3`
IL-10	Forward TCTCCGAGATGCCTTCAGCAGA Reverse TCAGACAAGGCTTGGCAACCCA
IL-18	Forward GATAGCCAGCCTAGAGGTATGG Reverse CCTTGATGTTATCAGGAGGATTCA
GAPDH	Forward GTCTCCTCTGACTTCAACAGCG Reverse ACCACCCTGTTGCTGTAGCCAA

2.5 Statistical analysis: The data of this study analysis by Statistical Package for Social Sciences (SPSS) version 26.0 for Windows. The data expressed as the mean ± standard error (SE). The p-value serves to denote statistical significance. Data are deemed significant when $p \leq 0.05$ or $p \leq 0.0001$.

One-way ANOVA tests employed to assess the statistical significance of the mean differences across the three groups. A ROC curve (receiver operating characteristic curve) conducted to evaluate the specificity and sensitivity of gene expression and to ascertain its role in the disease.

3. Results

Ninety participant in this study male (50%) and female (50%) dividing into 3 groups, N-*Hp* G 41.1%, G 25.6% and control 33.3%,median age 43 year . Non-significant different in age and gender between groups ($p > 0.05$).

Result of estimated gastritis: the *H. pylori* IgG antibody for N-*Hp* G.T2DM (215.72±3.57) high significant when compare to G (99.36±1.60) and control (98.02±0.98) the p-value <0.0001 that mean the patient have old infection with *H. pylori*. The level of hs-CRP following the same pattern of IgG. Hs-CRP levels found to be (8.04± 0.29 & 5.37±0.27) for N-*Hp* G.T2DM and G respectively ($p<0.0001$), control (5.33± 0.21) as shown in Figure 1 which demonstrated role of hs-CRP in N-*Hp* G T2DM.

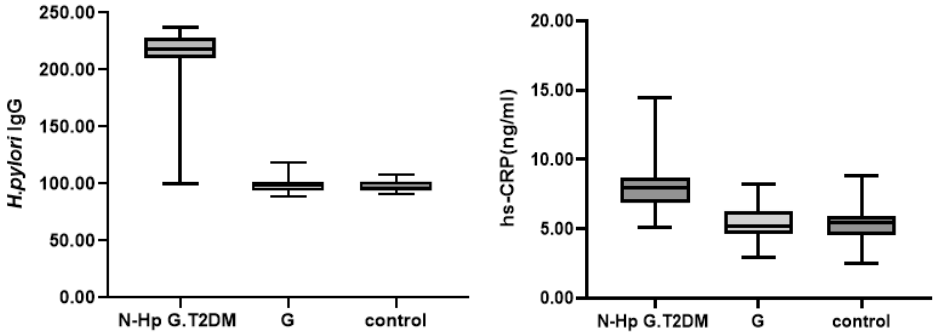


Figure (1): Means of *H.pylori* IgG (left) and hs-CRP (right) between study groups

T2DM estimation: via measure FBS and HbA1c in N-*Hp* G.T2DM (165.0±6.49, 8.85±0.24) statistically significant when compare with means of G (79.65±1.20, 5.37±0.27) and control (82.10±1.31, 4.56±0.04) p-value <0.0001 also HbA1C of G to control significant ($p < 0.05$).that indicator may be gastritis effect on metabolism and elevated sugar levels in blood. Furthermore BMI of N-*Hp* G.T2DM (25.23±0.39) significant with G (40.82=3.01) p-value< 0.0001 but not significant in comparison with control (22.62=0.35) p>0.05 (Figure 2).

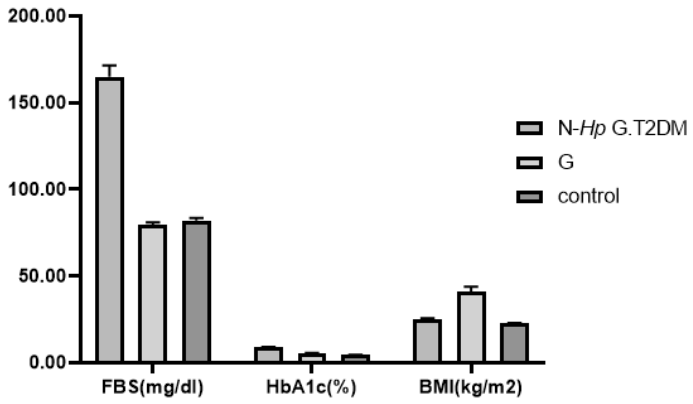
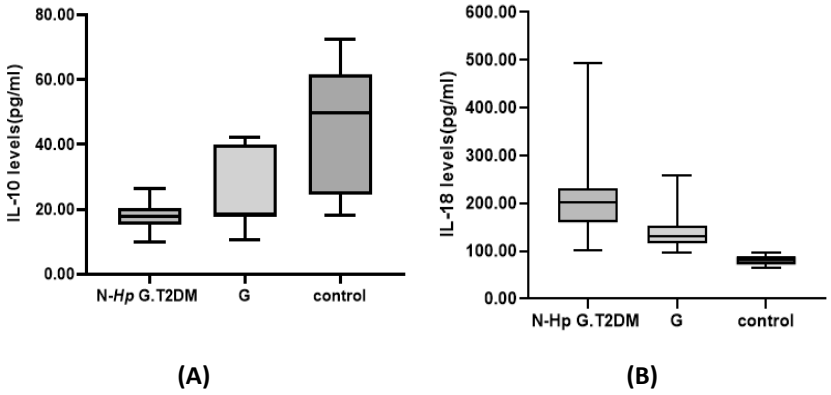


Figure (2): Histogram drown for FBS, HbA1C and BMI means observed samples of N-*Hp* G.T2DM, G and control groups

Interleukins estimated by ELIZA of all samples show opposite result. Found the anti-inflammatory IL-10 level decrease in N-*Hp* G.T2DM to (18.12±0.66) from (46.16±3.35) of control and group G also down to (25.28±2.46) p-value <0.05.On other hand IL-18 levels elevated in group N-*Hp* G.T2DM and G to (202.89±10.58 & 124.42±3.57) respectively from (81.00±1.80) of control p-value <0.0001. Figure 3 below showed the result.



(A) **(B)**

Figure (3): Compare means of IL-10 (A) and IL-18(B) levels between study groups

The result of gene expression of the IL-10 and IL-18 between the studies groups performed by using RT-qPCR and quantitative 2–ΔΔCT show IL-10 expression significant differences across the groups ($p<0.05$). Relative fold gene of N-*Hp* G.T2DM lowered from 1 (control) to 0.90 and to 0.75 in G group. Conversely, it was found that participants N-*Hp* G.T2DM relative expression of IL-18 (2.1575) was increased (Figure 4) in comparison to the control group (1.0025) ($p<0.01$). Similar trend among G group also demonstrating an increase in IL-18 levels (1.245) from (1.0025) control.

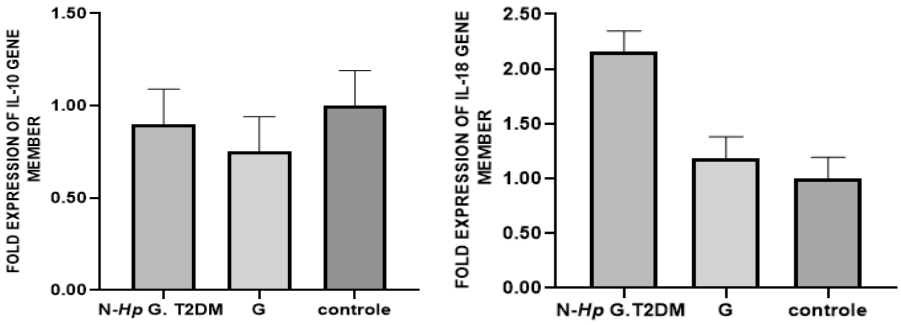


Figure (4): Comparison folding genes of IL-10 (left) and IL-18(right) gene expression between study groups.

The result of IL-10 and IL-18 Receiver Operating curve Characteristics: An evaluation of the link between IL-10 and IL-18 gene expression in N-*Hp* G. T2DM and the control group conducted using the Receiver Operating Characteristics (ROC) test. Findings the cut-off values of IL-10 were 72 and 98.7 for IL-18 and the p-value was very significant (p-value <0.0001. This suggests that the observed differences are not a consequence of random chance, additionally area under curve(AUC) very low in IL-10 (0.070) but excellent result in IL-18 (1), with a sensitivity of (0% and 100% respectively), and a specificity of (98% and 100% correspondingly) as illustrated in (Table 2) and (Figure 5).

Table 2: Roc curve analysis of IL-10 and IL-18 between N-*Hp* G.T2DM and control group

Test	Area Under Curve	cutoff	SE	P-value	Asymptotic 95% C.I		Sensitivity	Specificity
					Lower Bound	Upper Bound		
IL10	.070	72	.025	.000	.021	.120	0	98
IL18	1.000	98.7	.000	.000	1.000	1.000	100	100

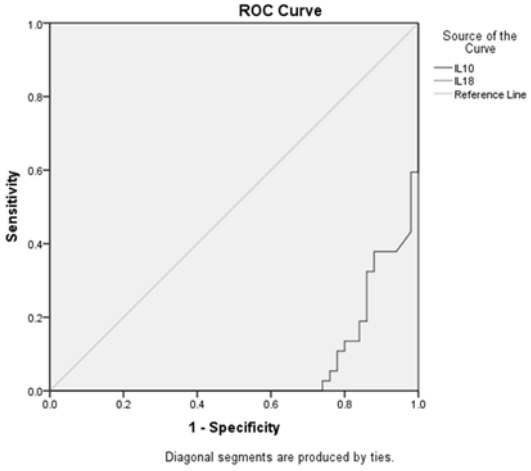


Figure 5: ROC for IL-10 and IL-18 in N-*Hp* G.T2DM

Table (3) and Figure (6) also revealed the relation of IL-10 and IL-18 in the G group by (ROC test). The area under the curve (AUC) for IL-10 was (.156), and (1.000) for IL-18 which is excellent according to (20), furthermore a highly significant (p-value <0.0001) in both interleukins. The cut-off for IL-10 was (73.5) and (96.2) for IL-18 as well as sensitivity (0% &100% respectively) and specificity (100% & 98%).

Table 3: Roc curve analysis of IL-10 and IL-18 between G and control group

Test	Area	cutoff	SE	P-value	Asymptotic 95% C.I		Sensitivity	Specificity
					Lower Bound	Upper Bound		
IL10	.156	73.5	.048	.000	.061	.250	0	100
IL18	1.000	96.2	.000	.000	1.000	1.000	100	98

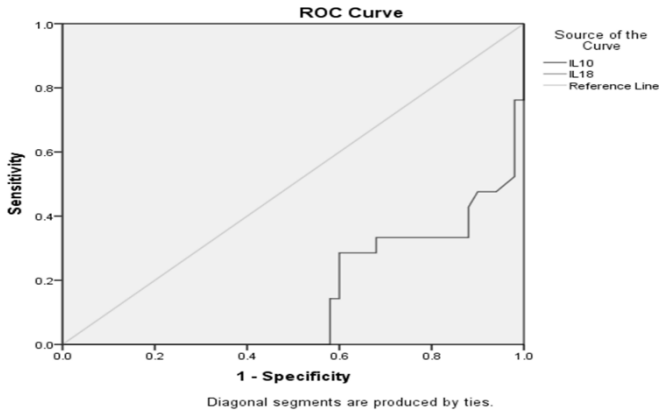


Figure 6: ROC for IL-10 and IL-18 in G group

4. Discussion

Inflammation of stomach is common in this time due to infection, diet, spread epidemics that weak immunity, autoimmune disease and taking non-steroidal anti-inflammatory drug(Kamada *et al*., 2022).Since patient with diabetic mellitus have low immunity are more susceptibility to inflammation (Scheithauer *et al*., 2020). A plethora of research has underscored the significance of inflammatory pathways and biomarkers in the context of diabetes and metabolic disorders. A cytokine constitutes one of these essential inflammatory indicators(Mansoor *et al*., 2022). Our research investigates the association between *H. pylori* infection and the levels of three pro-inflammatory cytokines (specifically IL-18 and IL-10) along with high sensitive C-reactive protein (hs-CRP), additionally *H.pylori* IgG levels in individuals with gastritis negative *H. pylori* and T2DM.The N-*Hp* G.T2DM show significant elevated *H. pylori* IgG Ab when compare to G and control . This due to old infection with *H. pylori* induce an immunological response, resulting in the synthesis of autoantibodies, which may be detectable even in individuals devoid of infection. In the context of autoimmune gastritis, individuals frequently exhibit heightened levels of autoantibodies in the absence of *H. pylori* infection, indicating a unique immunological mechanism in operation (Rugge *et al*., 2023). The hs-CRP significant increase in both N-*Hp* G.T2DM and G indicator about inflammation with diabetic mellitus (Ibrahim *et al*.).Fasting blood sugar and HbA1c high elevated in N-*Hp* G.T2DM because the subjects have diabetic but BMI level in this group not increase compare to G that significant elevated from normal .This due to loss of appetite and malabsorption in N-*Hp* G.T2DM patient. Since the interleukin play important role in inflammatory process therefor variation in their

concentration can used in predict abnormality (Al Bander *et al*., 2020). IL-10 level significant lower in N-*Hp* G.T2DM compare to G and control, indicator T2DM patients demonstrate a marked decrease in serum (IL-10) concentrations when juxtaposed with non-diabetic control subjects. There by indicating a possible involvement of this cytokine in the inflammatory mechanisms associated with the disease (Mitra *et al*., 2021). Moreover, IL-10 plays a pivotal role in modulating inflammatory responses, and its diminished levels may have implications for gastric pathologies however, there is a dearth of specific investigations focusing on non-*H.pylori* gastritis (Kim *et al*., 2012). While IL-18 level significant elevated in N-*Hp* G.T2DM than G and control, due to IL-18 linked to persistent inflammation, which serves as a significant determinant of insulin resistance and the advancement of Type 2 Diabetes Mellitus (Zatterale *et al*., 2020). Gene expression of IL-10 such concentration in ELIZA low in N-*Hp* G.T2DM and downregulation compare with G and control (Dos Santos Haber *et al*., 2022). Opposite gene expression of IL-18 gene that show upregulation in N-*Hp* G.T2DM patient (Bagheri *et al*., 2014). In ROC evaluations, IL-18 demonstrates robust diagnostic potential with elevated sensitivity and specificity. This makes it a dependable indicator for differentiating between N-*Hp* G.T2DM and control group, as well as the G group with control (Badr *et al*., 2021).On the other hand, IL-10 has a sensitivity of zero; therefore, it is not effective in correctly recognizing true positives, even though it has perfect specificity. This indicates that IL-10 is effective in correctly identifying negative results, but it is unable to detect any positive results in both the N-*Hp* G.T2DM and G groups in this particular scenario.

5. Conclusion

The patients with N-*Hp* G.T2DM significant elevated levels (p-value<0.05) of *H.pylori* IgG Ab, hs-CRP, FBS, HbA1c, IL-18 concentration and gene expression. Furthermore, decrease IL-10 concentration and gene expression.

6. References

- AL BANDER, Z., NITERT, M. D., MOUSA, A. & NADERPOOR, N.)2020(. The gut microbiota and inflammation: an overview. *International journal of environmental research and public health,* 17, 7618.
- BADR, M. T., OMAR, M. & HÄCKER, G.)2021(. Comprehensive integration of genome-wide association and gene expression studies reveals novel gene signatures and potential therapeutic targets for Helicobacter pylori-induced gastric disease. *Frontiers in Immunology,* 12, 624117.
- BAGHERI, N., RAHIMIAN, G., SALIMZADEH, L., TAGHIKHANI, A., MAHSA, M., HASHEMZADEH, M., AZADEGAN-DEHKORDI, F., SOLIMANI, N. & SHRZAD, H.) 2014(. Expression of IL-18 cytokine mRNA in gastric mucosa tissue of patients with H. pylori infection in Chahar Mahal and Bakhtiari. *Iranian South Medical Journal,* 17, 533-541.
- CHEN, L., CHEN, R., WANG, H. & LIANG, F.)2015(. Mechanisms linking inflammation to insulin resistance. *International journal of endocrinology,* 2015, 508409.
- DEFRONZO, R. A., FERRANNINI, E., GROOP, L., HENRY, R. R., HERMAN, W. H., HOLST, J. J., HU, F. B., KAHN, C. R., RAZ, I. & SHULMAN, G. I.)2015(. Type 2 diabetes mellitus. *Nature reviews Disease primers,* 1, 1-22.
- DOS SANTOS HABER, J. F., CHAGAS, E. F. B., BARBALHO, S. M., SGARBI, J. A., HABER, R. S. A., DE LABIO, R. W. & PAYÃO, S. L. M.)2022(. Level of physical activity and gene expression of IL-10 and TNF-α in children and adolescents with Type 1 diabetes. *J Diabetes Complications,* 36, 108104.
- EBULE, I., DJUNE, F., NJEAMBOSAY, B., DOH, G. & BEFOLO, M.)2017(. Atrophic gastritis and gastric cancer risk amongst diabetes mellitus type 2 subjects and controls in Yaounde Cameroon using a panel of serum biomarkers (PGI, G-17). *J Clin Gastroenterol Treat,* 3, 052.
- ELSEWEIDY, M.)2017(. Brief review on the causes, diagnosis and therapeutic treatment of gastritis disease. *Altern Integr Med,* 6, 1-6.

- GABRYŠOVÁ, L., HOWES, A., SARAIVA, M. & O'GARRA, A.)2014(. The regulation of IL-10 expression. *Interleukin-10 in Health and Disease*, 157-190.
- IBRAHIM, K. S., MUBARAK, K. I. & SALEH, M. A. D.(2020). IMMUNO-PATHOGENESIS OF HELICOBACTER PYLORI AND DIABETES MELLITUS TYPE II.
- KAMADA, T., MARUYAMA, Y., MONOBE, Y. & HARUMA, K.)2022(. Endoscopic features and clinical importance of autoimmune gastritis. *Dig Endosc,* 34, 700-713.
- KIM, J., CHO, Y. A., CHOI, I. J., LEE, Y.-S., KIM, S.-Y., SHIN, A., CHO, S.-J., KOOK, M.-C., NAM, J. H. & RYU, K. W.)2012(. Effects of interleukin-10 polymorphisms, Helicobacter pylori infection, and smoking on the risk of noncardia gastric cancer. *PloS one,* 7, e29643.
- LI, G., ZHU, L., CAO, Z., WANG, J., ZHOU, F., WANG, X., LI, X. & NIE, G.)2018(. A new participant in the pathogenesis of alcoholic gastritis: Pyroptosis. *Cellular Physiology and Biochemistry,* 49, 406-418.
- MANSOOR, G., TAHIR, M., MAQBOOL, T., ABBASI, S. Q., HADI, F., SHAKOORI, T. A., AKHTAR, S., RAFIQ, M., ASHRAF, M. & ULLAH, I.) 2022(. Increased expression of circulating stress markers, inflammatory cytokines and decreased antioxidant level in diabetic nephropathy. *Medicina,* 58, 1604.
- MITRA, P., SURI, S., SAXENA, I., SHUKLA, R. K., SHUKLA, K. K. & SHARMA, P.)2021(. Downregulation of interleukin-10 receptor (IL-10R) along with low serum IL-10 levels in newly diagnosed type 2 diabetes mellitus patients. *Gene Reports,* 24, 101251.
- OKAMURA, T., IWAYA, Y., KITAHARA, K., SUGA, T. & TANAKA, E.)2018(. Accuracy of endoscopic diagnosis for mild atrophic gastritis infected with Helicobacter pylori. *Clinical Endoscopy,* 51, 362-367.
- RUGGE, M., BRICCA, L., GUZZINATI, S., SACCHI, D., PIZZI, M., SAVARINO, E., FARINATI, F., ZORZI, M., FASSAN, M. & DEI TOS, A. P.)2023(. Autoimmune gastritis: long-term natural history in naïve Helicobacter pylori-negative patients. *Gut,* 72, 30-38.
- RUTZ, S. & OUYANG, W.)2016(. Regulation of interleukin-10 expression. *Regulation of Cytokine Gene Expression in Immunity and Diseases*, 89-116.
- SCHEITHAUER, T. P., RAMPANELLI, E., NIEUWDORP, M., VALLANCE, B. A., VERCHERE, C. B., VAN RAALTE, D. H. & HERREMA, H.)2020(. Gut microbiota as a trigger for metabolic inflammation in obesity and type 2 diabetes. *Frontiers in immunology,* 11, 571731.
- ZATTERALE, F., LONGO, M., NADERI, J., RACITI, G. A., DESIDERIO, A., MIELE, C. & BEGUINOT, F.)2020(. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Frontiers in physiology,* 10, 1607.
- ZHUANG, H., HAN, J., CHENG, L. & LIU, S.-L.)2019(. A positive causal influence of IL-18 levels on the risk of T2DM: a mendelian randomization study. *Frontiers in Genetics,* 10, 295.