# Tracking Galectin-9 and Galectin-14 Production Levels in Type 2 Diabetics During Treatment with Anti Hyperglycemic Drugs

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**Abreact**

**Background:** Nearly 90 to 95 % of individual who suffer from diabetes have type 2 diabetes mellitus (T2DM). Generally, the body can generate the insulin in this type of diabetes, but it is failed in secretion the proper amount of insulin. This type of diabetes previously included insulin independent diabetes, or adult-onset diabetes. It is often resistant to the action of insulin, and caused by insulin resistance in the liver and skeletal muscle, increasing glucose production in the liver, over production of free fatty acids by fat cells and relative insulin deficiency.

**Materials:** ninety participants were included in the current study, depending on their health status, participants were classified into 70 patients with type 2 diabetes and 20 healthy control groups. Sandwich-ELISA method was applied to evaluate insulin, galectin-9 and galectin-14 in the study samples.

**Results:** The study indicated that there were no significant differences in BMI between the two sexes in the four study groups. Moreover; the study demonstrated that there is no direct effect of BMI on the type of defect that causes one of the sexes to develop T2DM.The results of the statistical analysis show that there are significant differences when comparing G1 and G3 together, while; the study showed the absence of significant differences when comparing the rest of the illness groups with each other, as well as, when comparing the three T2DM groups with the healthy control group. Outcomes of the current study indicated that galectin-9 levels were comparable in both sexes, as no statistical differences were recorded when galectin-9 levels were compared between the two sexes in the four studied groups. Likewise, no statistically significant differences were observed when comparing individuals of the same sex with their counterparts in the other groups, except the differences in the levels of this protein which recorded when comparing males in the first and third groups together. The statistical analysis of galectin-14 data showed that there were significant differences when comparing the first pathological group (G1) with the G2 ($p=0.024$) and G3 ($p=0.045$), respectively, in the same way, a significant increase in galactin-14 levels was observed in G2 compared to healthy people. While the study did not show significant differences when comparing the remaining diseased groups together, as well as when comparing the G1 and G3 with the control group. The highest concentration of galectin-14 (3534.300 pg/mL) was observed in the sample of a 52-year-old woman in G2, who has a family history of diabetes and was diagnosed with the disease 10 years before the current study, while the lowest value for this parameter (68.2 pg/mL) was illustrated in a 51-year-old woman in the control group which indicates the possibility of using galectin-14 in follow-up damage resulting from a decline in the efficiency of the pancreas in producing insulin, coinciding with the occurrence of insulin resistance in women more than in men.

**Conclusions:** Pancreatic beta cells are rich in galectin-9 and galectin-14, and damage of these cells leads to a decrease in these protein levels. Galectins-9 and 14 function as immune proteins whose production coincides with inflammatory arousal such as insulin resistance in diabetic patients. Galectin-9 and galectin-14 are important tools in distinguishing between type 2 diabetes caused by decreased insulin production due to a defect in pancreatic beta cells or diabetes caused by impaired insulin action due to insulin resistance.

**Key Words:** Galectin-9, Galectin-14, T2DM, Anti Hyperglycemic Drugs

## Introduction

Diabetes is a group of metabolic diseases in which glucose is not sufficiently absorbed by skeletal muscle cells and adipocytes for energy when blood glucose levels are high. This can be caused by the pancreas failing to produce enough insulin due to a defect in beta cells or insulin receptors skeletal muscle cells and adipocytes do not respond to insulin, resulting in abnormally high blood glucose levels. The inability of these cells to absorb glucose, their main energy source, can have potentially serious consequences. High blood sugar is accompanied by a group of long-term diseases, dysfunction and failure in various organs of the body, especially the heart, eyes, blood vessels, kidneys and nerves[1]. The problem of diabetes is increasing worldwide, and it is common among both sexes. The main factors responsible for this global problem are genetic disorder, behavioral and environmental risk

factors. Modifiable risk factors such as obesity and physical inactivity are major non-genetic determinants of diabetes[2].

Galectins were discovered around 1975 based on their galactoside-binding activity, in an attempt to find proteins that decode complex glycans on the cell surface involved in cell adhesion. They were identified and named in 1994 based on the conserved beta-galactoside. Galectins are a family of soluble proteins that are widely distributed in nature and bind to a variety of glycoproteins[3]. Galectins, which were initially called S-type lectins, are defined as lectins with galactose-binding capacity and conserved amino acid sequences that characterize Galectin. family. Fifteen members of this family have been identified and they all share the consensus amino acid sequence of approximately 130 amino acids specific to the carbohydrate recognition domain (CRD)[4], as well as the recently identified novel galectin (member 16)[5]. Galectins participate in critically important processes at the molecular and cellular levels in human dermal and extracutaneous tissues, and exert biological effects of paramount importance through their interactions with cytoplasmic and nuclear proteins and cell surface and extracellular components. The function of galectins varies depending on their tissue and sub cellular location, and their association with carbohydrates makes them a key player in many intracellular and extracellular processes where they bind to proteins and glycosylated lipids[6]. There is ample evidence that many galectin proteins are expressed on many different immune and inflammatory cells[4].

Galectin-9 displays a wide range of activities in the immune system through its interactions with carbohydrates found in multiple proteins including TIM-3, IgE, and CD40. Galectin-9 promotes Th2-biased immune responses, expansion of regulatory T cells (Treg) and memory T cells, and stem cell maturation. It inhibits the development or activity of type 1 helper cells (Th1)[7], T-17 helper cells (Th17)[8], natural killer (NK)[9] cells, natural killer T cells (NKT), and cytotoxic T cells (Th17). CD8+)[10]. Galectin-9 suppresses immune complex-induced inflammation by modulating Fc receptor expression on macrophages and by preventing IgE immune complex formation. It reduces disease severity in inflammatory disorders such as high-fat diet-induced liver disease, collagen-induced arthritis, viral myocarditis, experimental autoimmune encephalomyelitis (EAE) and rheumatoid arthritis. It also promotes the resolution of inflammation by promoting macrophage clearance of cells infected with mycobacteria[11].

Galectin-14 is also known as placental protein 13 (PPL-13), and is one of the lesser-known galectins. It is a prototype galectin with significant homology to galectin-13. Galectin-14 gene has been identified as **LGALS14** and is located within a group of galectin genes in region q13.2 of chromosome 19[12]. Although galectin-14 is mostly known for its expression in the placenta, studies in animal models have shown that galectin-14 is known expressed in the placenta, it is also expressed in eosinophils from sheep, where it is released from these cells in response to allergen stimulation, suggesting a role for galectin-14 in regulating eosinophil activity during allergic responses, however, their expression and role in the inflammatory process remain largely unknown[13].

## Materials and Methods

**Patients and healthy controls:** ninety participants were included in the current study, depending on their health status, participants were classified into 70 patients with type 2 diabetes and 20 healthy control groups.

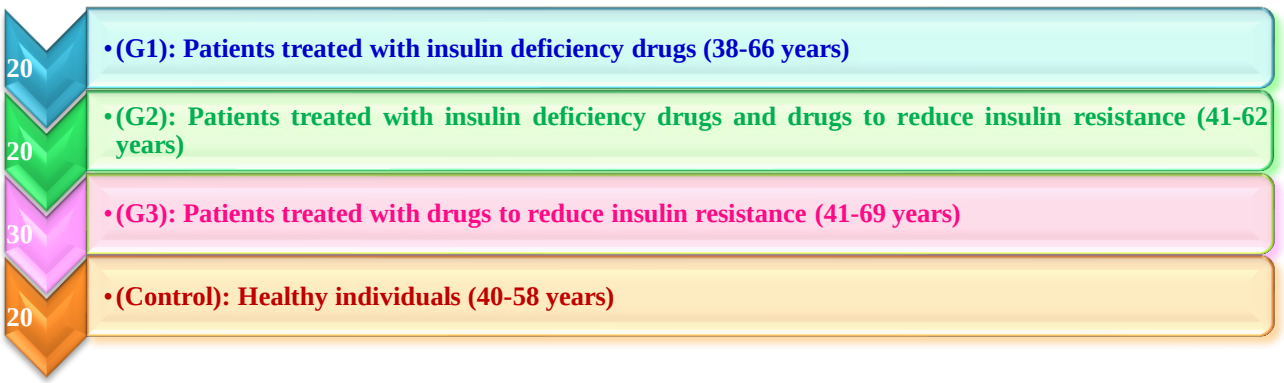


**Figure 1:Distribution of the Study Individuals Basing on their Health Status**

Cases of patients with type 2 diabetes were collected from the Diabetes and Endocrinology Center in Al-Sadr Medical City-Al Najaf Governorate. Healthy samples were collected from the study population environment, such as housewives, postgraduate students, as well as workers in the hospital where infected samples were also collected.

**Inclusion criteria of the patients and healthy controls:** the current study included individuals diagnosed as patients with type 2 diabetes and treated either with drugs to compensate for the decrease in the level of insulin produced, or patients treated with drugs to modify the affinity of insulin receptors, the hormone, or both types of treatments, provided that the patient does not suffer from the development of diabetes or the emergence of complications resulting from it. Healthy individuals were selected as a control group based on several criteria that included: they do not suffer from any type of diabetes or metabolic disorders, that they are of a similar age to the individuals in the patient group, that they have a dietary pattern similar to the individuals in the disease group, and that they do not take any medication. Finally, they look healthy.

**Exclusion criteria of the study:** the current study required exclusion of following cases, while the sufferers of the participating in the current study. Cases who underwent surgery within 5 years, smokers and alcohol drinkers.

**Samples Collection:** approximately at 9 AM in the morning, after at least 8 hours fasting, 5 milliliters of venous blood samples were collected from the type 2 diabetic patients and healthy individuals using gel tubes. After separating the serum from the study samples using a centrifuge at 5000 ×g for 5 minutes. Serum samples were preserved using Eppendorf tubes at -20°C after each sample was divided into 2 parts and stored until use. Sandwich-ELISA method was applied to evaluate galectin-9 and galectin-14in the study samples using human ELISA kitswhich furnished by Sun Long Biotech Com., LTD, China.

**Statistical Analysis:** the outcomes of the present study were analyzed through the statistical package for the social sciences (SPSS) version 26 software application statistical analysis system and excel (statistical package). The variables were illustrated by mean ± S.D, minimum, maximum, frequencies, and percentages. Graphics are presented using pie and bar charts. Inferential data analysis includes: One way analysis of variance (ANOVA) test was applied for examining the probable variations among the evaluated biochemicals. Pearson's correlation was applied to determine the relation among the biochemical parameters of the present study. The probability of deflection than controls are considered statistically significant if p-value is below 0.05.

## Results and Discussion

**Spotlight on the demographic characteristics of the study participants:** the present study included the participating of 90 individuals, who were divided into four groups, three of them (70 cases) were patients with previously documented type 2 diabetes mellitus (T2DM). The first illness group (G1) included 20 patients (10 males and 10 females) who were treated with insulin deficiency drugs only. The second group (G2) also included 20 patients (10 males and 10 females) who were treated with insulin deficiency drugs in addition to the drugs for reducing insulin resistance. While the third illness group (G3) included 30 patients (15 males and 15 females) who were treated with drugs to reduce insulin resistance. The last group included 20 healthy controls (10 males and 10 females).Demographic information indicates that all study patients underwent treatment to deal with the symptoms of type 2 diabetes, while members of the control group did not take any treatment during the period of obtaining the samples or before the start of the study, with emphasis on the fact that members of this group do not suffer from inflammatory diseases. The results in **Table 1** indicate that half of G1 members had a family history of diabetes in one or both parents, while the second group included 8 out of 20 patients with a family history, as for the group subject to treatment with drugs that improve the binding of the insulin hormone to its receptors (G3) included 14 out of 30 patients with a family history of diabetes. The study was based on the fact that the control group members had no history of diabetes. The study indicated that the period of diagnosis of the infection that preceded the start of the study ranged between one year and 30 years in general, while the highest infection period was in the first pathological group (individuals who suffer from a decrease in insulin production), while the shortest period was recorded G3. The statistical analysis indicated that there was a statistical difference in the period of diagnosis between G1 and G3 among patients, while the difference was not statistically acceptable comparing the period of infection in G1 and G2 or G2 and G3; respectively. Finally, it was noted that the

majority of T2DM patients participating in the current work are city residents, and this is consistent with previous studies that indicate that the city lifestyle induces diabetes[14].

**Table 1: Baseline Demographic Characteristics of The Participants in The Study**

| Parameters | Type 2 Diabetic Patients | | | Controls (n=20) |
|---|---|---|---|---|
| | G1 (n=20) | G2 (n=20) | G3 (n=30) | |
| Sex (Female / Male) | 10/10 | 10/10 | 15/15 | 10/10 |
| Treated/Untreated | 20/0 | 20/0 | 30/0 | - |
| Familiar History (Yes/No) | 10/10 | 8/12 | 14/16 | - |
| Duration of Disease (Year) (Mean± SD)<br>Minimum-Maximum | 13.200±7.046<br>3-23 | 12.650±7.322<br>2-30 | 9.100±5.732<br>1-22 | - |
| Rural/Urban | 3/17 | 1/19 | 1/29 | 0/20 |

**Topic of age and sex:** complete information on the age of participants in the current study were presented in **Table 2**. According to the results of one-way analysis of variance (ANOVA) test, no significant age difference was illustrated when compared G1 to both of G2 (p=0.118) and healthy control (p=0.086), same results were noted when G2 and G3 (p=0.695) were compared. While, statistically significant variations were noted when G1 and G3 compared (p=0.037) together, with the same manner, significant differences were shown when each of G2 and G3 compared to the control group (p<0.05).

**Table 2: Age (Years) of the Study Groups**

| Subjects (n) | Age (Years) Mean ± SD | Minimum-Maximum | p-value |
|---|---|---|---|
| G1 Patients (20) | 51.90±7.670 | 38-66 | 0.118 For G1 vs G2<br>0.037 For G1 vs G3<br>0.086 For G1 vs C<br>0.695 For G2 vs G3<br>0.001 For G2 vs C<br>0.000 For G3 vs C |
| G2 Patients (20) | 55.35±5.779 | 41-62 | |
| G3 Patients (30) | 56.13±7.999 | 41-69 | |
| Controls (20) | 48.10±5.119 | 40-58 | |

The results of the present work indicate that the life expectancy of T2DM patients with reduced insulin production only while maintaining the efficiency of its receptor (G1) was lower (51.9 years) compared to the rest of the patients. In the other two disease groups. While individuals in the group of patients treated with drugs that enhance the affinity of insulin molecules towards their receptors (G3) had the oldest average age (56.13 years) among the three groups of patients. The study showed that the oldest patient was a 69-year-old man in the third group, while the youngest patient was a 38-year-old woman in the first group. The main

feature of aging is the progressive loss of physiological integrity, which in turn leads to impaired function and increased susceptibility to mortality. This decline is the primary risk factor for the majority of human diseases including cancer, cardiovascular disorders, neuro-degeneration, and diabetes[4]. Diabetes is a common disease in the elderly, with approximately 50% of type 2 diabetes patients over the age of 60 years; despite this, half of older people with overt diabetes are not diagnosed. While insulin resistance is common in older adults, large numbers of them also have impaired insulin secretion. Age, body habits, and physical activity play a role in causing the high blood sugar associated with diabetes. Diet management plays a lesser role in older diabetics, but exercise, with particular emphasis on balance and stability, is an important component of the management and treatment of older diabetics. The study highlights the difficulty of finding healthy individuals according to the criteria for group selection control subjects, whose ages were close but not identical to the groups of three study patients. The reason for this is the difficulty of finding individuals in their sixth decade who do not suffer from any chronic or inflammatory diseases, and who have also not previously undergone surgical treatment. In order to evaluate the effect of gender on the incidence of type 2 diabetes and the level of response to medications used to treat symptoms of the disease, members of the study groups were divided into eight subgroups based on gender.

**Table 3: Age of the Study Subgroups**

| Subjects (n) | Sex (n) | Age (Years) Mean ± SD | Minimum-Maximum | p-value |
|---|---|---|---|---|
| G1 Patients (20) | Female 10 | 51.70±4.572 | 45-58 | 0.899 For 1 vs 2<br>0.975 For 3 vs 4 |
| | Male 10 | 52.10±10.159 | 38-66 | 0.277 For 5 vs 6<br>0.567 For 7 vs 8 |
| G2 Patients (20) | Female 10 | 55.30±4.832 | 47-62 | 0.254 For 1 vs 3<br>0.045 For 1 vs 5 |
| | Male 10 | 55.40±6.867 | 41-62 | 0.155 For 1 vs 7<br>0.437 For 3 vs 5 |
| G3 Patients (30) | Female 15 | 57.53±57.53 | 41-69 | 0.012 For 3 vs 7<br>0.001 For 5 vs 7 |
| | Male 15 | 54.73±8.031 | 43-68 | 0.296 For 2 vs 4<br>0.360 For 2 vs 6 |
| Healthy Controls | Female 10 | 47.20±3.706 | 42-53 | 0.326 For 2 vs 8<br>0.816 For 4 vs 6 |
| | Male 10 | 49.00±6.307 | 40-58 | 0.044 For 4 vs 8<br>0.048 For 6 vs 8 |

**When: 1,3,5,7 are refer to Female Subgroups in the G1, G2, G3 and Control Groups; respectively, while:2,4,6,8 are refer to Male Subgroups in the G1,G2,G3 and Control Groups; respectively.**

**Table 3** showed there are no significant differences between males and females in same group (regardless the health state or the treatment type), and this indicates that the age factor is not affected by the sex, so this means that any person can suffer from diabetics that lead to the necessity of using insulin-supplementing drugs only, and also insulin-supplementing drugs with the drugs that reduce insulin resistance together, or the drugs that reduce insulin resistance only; according to the dysfunction kind. Moreover, the statistical analysis showed there are no significant differences between healthy males and females when compared together. **Table 3** shows the absence of statistically significant differences when comparing between the sexes in one group (whether the disease group or the control group). This indicates that the age factor is not affected by the sex, which confirms the possibility of both sexes developing diabetes after the fourth decade, regardless of the type of defect the cause of hyperglycemia, whether it is a defect in insulin production or a disruption of its receptors. When comparing the subgroups of the same sex, it was noted that there were significant differences when comparing the females in the first group (G1) with their counterparts in the third group (G3), while the study did not record the same differences when comparing the females of the disease groups together. On the other hand, the study did not record any statistically significant differences when comparing males in the disease groups with each other. The current study recorded significant differences when comparing members of the second (G2) and third (G3) groups of both sexes with their peers of the same sex in the healthy control group.

**Highlight on the body mass index of the study individuals:** although the highest body mass index (BMI) was 42.824 Kg/m$^2$ for a woman in G1, the results of the current study indicated to the absence of statistical significance when comparing G1 and the control group, in contradiction to that result, the study showed a statistically significant increase for members of G2 (p=0.004) and G3 (p=0.049) when compared to the control group. The study found that mean BMI was very similar in the T2DM groups, so the study did not show significant differences when comparing the three groups together, as illustrated in **Table 4**.

**Table 4: Body Mass Index (Kg/m$^2$) of the Study Groups**

| Subjects (n) | BMI (Kg/m$^2$) Mean ± SD | Minimum-Maximum | p-value |
|---|---|---|---|
| G1 Patients (20) | 29.379±4.665 | 24.096-42.824 | 0.325 For G1 vs G2<br>0.878 For G1 vs G3<br>0.053 For G1 vs C<br>0.219 For G2 vs G3<br>0.004 For G2 vs C<br>0.049 For G3 vs C |
| G2 Patients (20) | 30.605±3.269 | 24.732-36.764 | |
| G3 Patients (30) | 29.205±4.291 | 19.921-39.190 | |
| Controls (20) | 26.945±2.980 | 21.453-31.250 | |

The study indicated that there were no significant differences in BMI between the two sexes in the four study groups, whether they were the three disease groups or the control group. In the same way, the study demonstrated that there is no direct effect of BMI on the type of defect that causes one of the sexes to develop T2DM, as the study did not record any statistical differences occurred when comparing individuals of the same sex in groups of diabetic patients with each other, or with their peers of the same sex in the control group, with the exception of the increase in BMI of females in the G2 compared to their counterparts in the control group, as shown in **Table 5.**

**Table 5: Body Mass Index of The Studied Subgroups**

| Subjects (n) | Sex (n) | BMI (Kg/m$^2$) Mean ± SD | Minimum-Maximum | p-value |
|---|---|---|---|---|
| G1 Patients (20) | Female 10 | 30.841±5.498 | 24.221-42.824 | 0.097 For 1 vs 2<br>0.250 For 3 vs 4<br>0.656 For 5 vs 6 |
| | Male | 27.917±3.312 | 24.096-33.422 | |

| | | | | |
|---|---|---|---|---|
| | 10 | | | 0.535 For 7 vs 8 |
| | Female 10 | 31.616±2.907 | 27.553-35.714 | 0.658 For 1 vs 3<br>0.410 For 1 vs 5 |
| G2 Patients (20) | Male 10 | 29.594±3.441 | 24.732-36.764 | 0.058 For 1 vs 7<br>0.193 For 3 vs 5 |
| | Female 15 | 29.523±3.640 | 24.979-37.698 | 0.020 For 3 vs 7<br>0.205 For 5 vs 7 |
| G3 Patients (30) | Male 15 | 28.886±4.967 | 19.921-39.190 | 0.339 For 2 vs 4<br>0.544 For 2 vs 6 |
| | Female 10 | 27.489±2.887 | 23.437-31.250 | 0.388 For 2 vs 8<br>0.658 For 4 vs 6 |
| Controls | Male 10 | 26.402±3.124 | 21.453-31.141 | 0.071 For 4 vs 8<br>0.123 For 6 vs 8 |

The current study indicates that there is no strong correlation between the BMI and the incidence of T2DM, this result is in contradiction to most studies conducted on the subject[16]. The reason for this finding may be attributed to the fact that the BMI of the patients in the study groups did not reach the morbid obesity, on the other hand, although the individuals in the control group were free of diseases and appeared to be healthy, their average BMI was slightly higher than ideal, and this caused a deviation in the results obtained from what is prevalent in this field. The results of the current study agreed with the Nirupoma, et al., study, which indicated that only 37% of patients with T2DM who were between the ages of 30 and 60 years were obese, while this percentage decreased to only 12% for patients in their seventh decade[15] .

**Levels of Galectin-9 in the Study Groups:** the levels of galectin-9 were evaluated in the study samples, it was found that the highest mean of galectin-9 (22.941 pg/mL) was recorded in G3, while its lowest levels (15.360 pg/mL)was noted in G1. The results of the statistical analysis show that there are significant differences when comparing G1 and G3 together, while; the study showed the absence of significant differences when comparing the rest of the illness groups with each other, as well as, when comparing the three T2DM groups with the healthy control group, as demonstrated in **Table 6**.

**Table 6: Levels of Galectin-9 (pg/mL) in the Diabetic Patients and Controls Groups**

| Subjects (n) | Galectin-9 (pg/mL) Mean ± SD | Minimum-Maximum | p-value |
|---|---|---|---|
| G1 Patients (20) | 15.360±6.823 | 6.592-34.063 | 0.277 For G1 vs G2<br>0.006 For G1 vs G3<br>0.291 For G1 vs C<br>0.107 For G2 vs G3<br>0.976 For G2 vs C<br>0.101 For G3 vs C |
| G2 Patients (20) | 18.575±9.850 | 3.875-47.848 | |
| G3 Patients (30) | 22.941±11.417 | 4.919-46.203 | |
| Controls (20) | 18.487±6.989 | 7.808-37.380 | |

The results of the current study which shown in **Table 7** indicated that galectin-9 levels were comparable in both sexes, as no statistical differences were recorded when galectin-9 levels were compared between the two sexes in the four studied groups. Likewise, no statistically significant differences were observed when comparing individuals of the same sex with their counterparts in the other groups, except the differences in the levels of this protein which recorded when comparing males in the first and third groups together.

**Table 7:Levels of Galectin-9 (pg/mL) in the Diabetic Patients and Controls Subgroups**

| Subjects (n) | Sex (n) | Galectin-9 (pg/mL) Mean ± SD | Minimum-Maximum | p-value |
|---|---|---|---|---|
| G1 Patients | Female10 | 16.172±7.670 | 6.592-34.063 | 0.704 For 1 vs 2 |

| | | | | |
|---|---|---|---|---|
| (20) | Male10 | 14.549±6.164 | 8.265-24.110 | 0.852 For 3 vs 4 |
| G2 Patients (20) | Female10 | 18.973±12.788 | 4.476-47.848 | 0.852 For 5 vs 6<br>0.875 For 7 vs 8 |
| | Male10 | 18.178±6.398 | 3.875-25.955 | 0.512 For 1 vs 3 |
| G3 Patients (30) | Female15 | 23.266±11.750 | 4.919-40.927 | 0.071 For 1 vs 5 |
| | Male15 | 22.618±11.476 | 5.220-46.203 | 0.535 For 1 vs 7<br>0.272 For 3 vs 5 |
| Controls (20) | Female10 | 18.822±5.477 | 8.537-25.311 | 0.972 For 3 vs 7 |
| | Male10 | 18.152±8.537 | 7.808-37.380 | 0.256 For 5 vs 7<br>0.396 For 2 vs 4<br>0.041 For 2 vs 6<br>0.399 For 2 vs 8<br>0.256 For 4 vs 6<br>0.995 For 4 vs 8<br>0.253 For 6 vs 8 |

Likewise, no statistically significant differences were observed when comparing individuals of the same sex with their counterparts in the other groups, except the differences in the levels of this protein which recorded when comparing males in the first and third groups together.

Galectin-9 is stimulated and released from various cells by interferon-γ in human endothelial cells, fibroblasts, pancreatic β cells, and Kupffer cells. Galectin-9 is vulnerable to digestion by proteolytic degradation; however, it was reported that galectin-9 is inserted into exosome and released, thus it is protected by enzymatic degradation, and the intact 36 kDa molecule was demonstrated in the serum exosome fraction[17]. Galectin-9 may act as an essential cell-cycle regulator, the cell cycle is dysregulated in the diabetic state, and G1-phase arrest is believed to be responsible for the high glucose induced cellular hypertrophy and increase in the de novo protein synthesis and consequential accumulation of extracellular matrix proteins.Galectin-9 promotes and assists cell-cycle progression and successful replication in diabetic state, where cell-cycle progression is halted despite cellcycle entry. Thus, galectin-9 exerts dual action on the cells and modulates the fate of cells, i.e., apoptosis subsequent to S-phase arrest or successful progression to G2 phase depending on the status or the nature of the cells.Galectin-9 is a protein expressed mainly in the liver, small intestine, and thymus. The half-life of galectin-9 is short, ranging from 30 to 60 min. It has been discovered as a potential auto-antigen in Hodgkin's lymphoma, possibly affecting the regulation of immune processes[15]. Galectin-9, like other galectins, plays a role in regulating cell proliferation, differentiation, and apoptosis. It binds to mucin domain-3, a receptor expressed in T cells, monocytes, and natural killer cells, inducing apoptosis to deescalate immune responses. Galectin-9 expression has been shown to increase in subcutaneous adipose tissue and in macrophages of visceral adipose tissue in obese mice, as well as in the serum of patients with T2DM[15]. Recent studies have focused on the role of galectin-9 in the pathophysiology of T2DM[16]. Sun et al., evaluated the role of galectin-9 in the pathogenesis of T2DM, especially obesity-related. The concentration of galectin-9 in the serum of subjects with obese T2DM was significantly higher than in healthy individuals and in the mild obesity group. Moreover, the galectin-9 level in the obese T2DM patient group was positive it binds to fasting insulin and C-peptide, two clinical features that account for pancreatic islet function in T2DM[19]. The results of the current work are consistent with previous studies that focused on the fact that levels of galectin-9 decrease in patients with T2DM compared to healthy people, unless the disease progresses to the stage of the appearance of its resulting complications. As for the statistical differences observed when comparing G1 and G3, it may be explained that the high blood sugar levels may be due to the inflammatory state coinciding with the resistance of cells to insulin and the advanced age of patients in this group, and this is consistent with the hypotheses of Hiroko Iwasaki, et al., N. Giovannone, et al., and others.

**Levels of Galectin-14 in the Type 2 Diabetic Patients and Healthy Individuals:** the results of the statistical analysis of galectin-14 data showed that there were significant differences when comparing the first pathological group (G1) with the G2(p=0.024) and G3 (p=0.045), respectively, in the same way, a

significant increase in galactin-14 levels was observed in G2 compared to healthy people. While the study did not show significant differences when comparing the remaining diseased groups together, as well as when comparing the G1 and G3 with the control group, as noted in **Table 8**.

**Table 8: Levels ofGalectin-14 (pg/mL) in Type 2 Diabetic and Control Groups**

| Subjects (n) | Galectin-14 (pg/mL)Mean ± SD | Minimum-Maximum | p-value |
|---|---|---|---|
| G1 Patients (20) | 729.190±552.558 | 231.000-2410.100 | 0.024 For G1 vs G2<br>0.045 For G1 vs G3<br>0.775 For G1 vs C<br>0.779 For G2 vs G3<br>0.041 For G2 vs C<br>0.818 For G3 vs C |
| G2 Patients (20) | 919.600±938.008 | 128.700-3534.300 | |
| G3 Patients (30) | 854.847±791.977 | 158.400-3163.600 | |
| Controls (20) | 801.625±858.008 | 68.200-3060.200 | |

With the exception of the apparent statistical differences between the sexes in the second group (G2), the study did not show any significant differences when comparing the sexes in one group (whether it was a group of diabetic patients or healthy people).The study demonstrated the presence of significant differences only when comparing women in the second group with their counterparts in the third group and the control group, and the same results were observed when comparing men in the second and third groups, while the results lacked significance when implicitly comparing subgroups of the same sex with each other, as shown in **Table 9**. The highest concentration of galectin-14 (3534.300 pg/mL)was observed in the sample of a 52-year-old woman in G2, who has a family history of diabetes and was diagnosed with the disease 10 years before the current study, while the lowest value for this parameter (68.2 pg/mL) was illustrated in a 51-year-old woman in the control group which indicates the possibility of using galectin-14 in follow-up damage resulting from a decline in the efficiency of the pancreas in producing insulin, coinciding with the occurrence of insulin resistance in women more than in men.

**Table 9:Levels ofGalectin-14 (pg/mL) in Type 2 Diabetic and Control Subgroups**

| Subjects (n) | Sex (n) | Galectin-14 (pg/mL)Mean ± SD | Minimum-Maximum | p-value |
|---|---|---|---|---|
| G1 Patients (20) | Female 10 | 686.620±456.924 | 261.800-1774.300 | 0.807 For 1 vs 2<br>0.013 For 3 vs 4<br>0.156 For 5 vs 6<br>0.781 For 7 vs 8<br>0.056 For 1 vs 3 |
| | Male 10 | 771.760±657.084 | 231.000-2410.100 | |
| G2 Patients | Female | 1359.490±1158.559 | 341.000-3534.300 | |

| | | | | |
|---|---|---|---|---|
| **(20)** | **10** | | | **0.913 For 1 vs 5** |
| | **Male 10** | **479.710±291.916** | **128.700-1060.400** | **0.849 For 1 vs 7** |
| | | | | **0.028 For 3 vs 5** |
| **G3 Patients (30)** | **Female 15** | **651.713±460.478** | **205.700-1723.700** | **0.045 For 3 vs 7** |
| | | | | **0.750 For 5 vs 7** |
| | **Male 15** | **1057.980±999.397** | **158.400-3163.600** | **0.403 For 2 vs 4** |
| | | | | **0.370 For 2 vs 6** |
| **Controls (20)** | **Female 10** | **753.170±928.219** | **68.200-3060.200** | **0.822 For 2 vs 8** |
| | | | | **0.042 For 4 vs 6** |
| | **Male 10** | **850.080±829.064** | **206.800-2614.700** | **0.290 For 4 vs 8** |
| | | | | **0.514 For 6 vs 8** |

Although galectin-14 is mostly known for its expression in the placenta[20], it is also expressed in eosinophils, where it is released from these cells in response to allergen stimulation, suggesting a role for galectin-14 in regulating eosinophil activity during allergic responses. Lorena, et al., found that high expression of galectin-14 mRNA in ovarian cancer cells is associated with shorter survival[13]. The study showed an increase in the level of galectin-14 in patients in the second group, and this increase may be due to increased gene expression of other lectins that coincide with the inflammatory state, as is the case in type 2 diabetes, especially those treated with decreased insulin production and disruption of its function. Based on investigations in the literature, no previous work was found to study galectin-14 levels in patients with type 2 diabetes, or in more detail to evaluate galectin-14 levels in patients treated with medications to treat various conditions causes of high blood sugar, so the current study is considered the first of its kind in this field.

## Conclusion

Pancreatic beta cells are rich in galectin-9 and galectin-14, and damage of these cells leads to a decrease in these protein levels. Galectins-9 and 14 function as immune proteins whose production coincides with inflammatory arousal such as insulin resistance in diabetic patients. Galectin-9 and galectin-14 are important tools in distinguishing between type 2 diabetes caused by decreased insulin production due to a defect in pancreatic beta cells or diabetes caused by impaired insulin action due to insulin resistance.

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