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# Investigation the role of GDF-15 and ARFIP2 Levels in Type 2 Diabetic Patients A Comparative Gender-Based Study

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**ABSTRACT**

***Objective:*** *The present study seeks to evaluate the quantification of serum levels of ADP-ribosylation factor-interacting protein 2 (ARFIP2) and growth differentiation factor-15 (GDF-15), as well as to investigate potential correlations between these factors and glycaemic control metrics and insulin resistance (HOMA-IR), in order to elucidate their roles in the pathophysiology and progression of diabetes mellitus (DM).* ***Method:*** *The case-control study included 111 individuals, consisting of 51 patients diagnosed with diabetes mellitus and 60 healthy individuals serving as a control group. We measured the levels of GDF-15 and ARFIP2 in two study groups, as well as the levels of serum glycaemic markers (FBS, Insulin, HbA1c) and HOMA-IR.* ***Results:*** *In T2DM, ARFIP2 showed significant correlations with FBS, insulin, and HOMA-IR suggesting its role in insulin resistance and acute glycemic regulation but showed limited associations in controls, indicating its role becomes more pronounced under diabetic conditions. GDF-15 showed a positive but non-significant correlation with ARFIP2, hinting at a possible shared pathway in metabolic stress and inflammation but in control group showed a highly significant correlation suggesting it may act as an early biomarker of metabolic stress.* ***Novelty:*** *ARFIP2 is strongly associated with insulin resistance and acute glycemic markers in T2DM, but not with long-term glycemic control. GDF-15 shows strong associations in controls and trends in T2DM, suggesting it may serve as an early stress-response biomarker. Gender differences in distribution were observed but not statistically significant, indicating the need for larger sample sizes to clarify gender-specific biomarker patterns.*

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder marked by hyperglycemia due to insulin secretion and action defects. Chronic hyperglycemia leads to organ damage, increased mortality, and reduced quality of life. Low-carbohydrate diets may aid in diabetes treatment [1]. In Iraq, diabetes, particularly type 2 DM, poses an emerging public health crisis with escalating numbers of affected individuals. Urbanization and dietary changes are two important factors that lead to obesity [2], [3]. Type 2 Diabetes Mellitus (T2DM) affects one in 11 adults around the world, and more than 80% of those with it live in low- to middle-income countries. Because it is becoming more common and has serious complications, especially for people with low incomes, it is a major global health problem. In adults aged 45 to 55, the prevalence can exceed 25%, frequently resulting in delayed diagnoses and unregulated blood glucose levels, thereby elevating the risks for kidney disease, blindness, amputations, and premature mortality. Also, T2DM is a big risk element for stroke and heart disease [4].

Growth differentiation factor-15 (GDF-15) is a cytokine that responds to stress and is part of the transforming growth factor-β (TGF-β) superfamily. Also, it is involved in inflammation, the cellular stress response, and the control of metabolism. High levels of

GDF-15 have been linked to insulin resistance, heart problems, and the worsening of diabetes. This makes it a possible biomarker for the severity and outlook of the disease [5].

GDF15 is robustly induced in times of cellular stress, including mitochondrial dysfunction, hypoxia, inflammation, and oxidative stress, accompanied by reactive oxygen species (ROS) production [6], [7].

Circulating GDF15 is recognized as a biomarker in cardiovascular diseases, diabetes, obesity, fatty liver (non-alcoholic) diseases, in addition cancer. Its association with kidney function, injury, fibrosis, and diseases has been confirmed, impacting sex-specific renal pathology. GDF15 protects against acute and chronic renal injury, linking mitochondrial dysfunction, obesity, and diabetes to renal fibrogenesis [8].

A protein involved in actin cytoskeleton remodeling and vesicular trafficking ADP-Ribosylation Factor-Interacting Protein 2 (ARFIP2). Recent evidence suggests its role in insulin signaling and glucose metabolism, though its exact contribution to T2DM pathophysiology remains underexplored [9]. Its role in metabolic and genetic conditions like in Type 2 Diabetes Mellitus; through its role in autophagy and vesicle trafficking, ARFIP2 may influence insulin signaling and cellular stress responses [10]. Also, in hyperprolinemic Type 1; though the connection is less direct, ARFIP2 has been listed among genes associated with this metabolic disorder [11].

There are well-known differences between men and women with T2DM, such as how common the disease is, how it affects people, and how biomarkers are expressed. Hormonal influences, genetic predispositions, and lifestyle factors contribute to these disparities [12]. The aims of the study were explore the association of GDF-15 and ARFIP2 with T2DM progression, assess whether their expression levels differ significantly between male and female patients, contribute to the understanding of gender-specific pathophysiological mechanisms in T2DM, and explore the potential correlations among GDF-15, ARFIP2 and glycemic markers to clarify their roles in the pathophysiology and progression of diabetic mellitus.

## RESEARCH METHOD

The current work used a study case control design. This study incorporated patients who visited Al-Fayhaa Teaching Hospital and General Al- Almawani Hospital in Basrah's governorate; the sample was taken in the duration of March 2025 to June 2025. The study population comprised 51 patients with DM. Further, there will be 60 apparently healthy person serving as a control group.

**Exclusion criteria:**

Patients who had a history of autoimmune or inflammatory disease, cancer, immunosuppression, were excluded from the analysis since these disorders had the potential to independently alter the parameters of the study.

**Sample collection:**

A total of 10 ml of blood was drawn from each patient and control group 5ml placed in sterile gel tubes and allowed to coagulate at room temperature (25C) for 10 minutes

before being separated by centrifuge for fifteen minutes at a speed of three thousand rpm to separate the serum and another 5ml of blood placed in EDTA tubes. The serum and the blood should be kept at -20C until use.

**Methodology:**

The serum evaluations of GDF-15 and ARFIP2 were done using ELISA and were conducted according to the guidelines provided by the manufacturer of the kit (BT LAB, China). The levels of routine serum biomarkers (RBS and Insulin) in accordance with the manufacturer's instructions of (Roche Diagnostic, Germany) and HbA1c in accordance with the manufacturer's instructions of (BIO-RAD, USA).

**Statistical analysis:**

For the purpose of statistical analysis, SPSS, version 6, was used. Qualitative data were expressed in terms of number and percentage, while quantitative data were expressed as Mean± SD and Median with minimum – maximum values. To test for the distribution of data, whether parametric or nonparametric, Shapiro Willk and Kolmogorov Smirnov tests were applied. To investigate for statistical relationships between qualitative variables, $Ch^2$ test was used and to investigate the differences between quantitative variables, Mann Whitney U Test was used. Also, to explore the presence of correlations among both of the quantitative variables, Spearman correlation test was used. An association, difference, or correlation of a p-value of less than 0.05 was considered significant.

## RESULTS AND DISCUSSION

**The frequency and percentage categories of two groups:**

As show in table 1 this study appeared that there is no significant statistical difference in gender distribution between T2DM and control. Compared to the healthy control group the proportion of males is slightly higher in diabetic mellitus group. The healthy control group has an equal number of men and women, which could mean that the recruitment or population baseline is more balanced.

**Table 1.** The percentage and frequency categories of T2DM and control according to sex.

| Gender | | Category | | | |
|---|---|---|---|---|---|
| | | T2DM | control | Total | P value* |
| Sex | Male | 33<br>64.7% | 30<br>50.0% | 63<br>58.4% | 0.241 |
| | Female | 18<br>35.3% | 30<br>50.0% | 48<br>41.6% | |
| Total | | 51<br>100.0% | 60<br>100.0% | 111<br>100.0% | |

* Chi-Square Test

Some studies indicate that men are more prone to early diagnosis and treatment of diabetes-related complications due to healthcare-seeking behaviors, resulting in a higher

male representation in clinical datasets, despite potentially similar disease burden across genders [13], [14].

Another study of 1,549 T2DM patients demonstrated that females had a significantly higher frequency of diabetes mellitus (17.3%) than males (12.6%), with a cumulative risk ratio of 1.33 (P = 0.034) [15]. This statistic does not hold true for the present study dataset. These findings suggest that females may be underdiagnosed or under-represented in T2DM cohorts despite greater biological risk. This difference raises doubts about gender-sensitive screening protocols and longitudinal studies that monitor progression by sex.

**Routine parameters of the T2DM patients and controls compared.**

Concerning Fasting Blood Sugar, Insulin and HOMA-IR, they were highly increased in patients with diabetes (p= 0.0001) which is typical of insulin resistance and hyperglycemia. Furthermore, Higher HbA1c is a pointer of poor long-term glycemic control of diabetics.

**Table 2.** Routine parameters of the T2DM patients and controls compared.
***Mann Whitney U Test**

| Parameter | Groups | | | | P. value* |
|---|---|---|---|---|---|
| | T2DM (n=51) | | Control (n=60) | | |
| | Mean± SD | Median Min-Max | Mean± SD | Median Min-Max | |
| **FBS (mg/dl)** | 218.5 ± 49.45 | 200.0 150-400 | 88.85 ± 4.381 | 89.50 80-100 | 0.0001 |
| **Insulin (µIU /ml)** | 16.17 ± 3.486 | 16.20 9.2-26.1 | 7.272 ± 2.102 | 7.10 4.2-14.4 | 0.0001 |
| **HOMA-IR** | 8.757 ± 3.133 | 8.200 3.6-17.8 | 1.568 ± 0.5267 | 1.500 0.9-3.5 | 0.0001 |
| **HbA1c (%)** | 9.267 ± 2.280 | 8.900 5.4-14.5 | 5.297 ± 0.4241 | 5.200 4.2-6.3 | 0.0001 |

However, according to a study in 2020, T2DM patients had high glucose, insulin, and HOMA-IR levels, which are in line with the current data (Long et al). Other reports also indicated that overall and abdominal obesity have a causal relationship with insulin resistance, fasting glucose, and HbA1c [16], [17].

However, one of the studies conducted by Chung *et al.* contradicts the existing evidence as it underlines the idea that glycemic variability, social determinants of health, and individualized treatment make the situation with hyperglycemia more complicated and states that not all patients with T2DM have higher glucose or insulin levels at the time of diagnosis, but their postprandial glycaemic control or insulin sensitivity is defective [18].

The current study achievement is matched by a study conducted by Gu et al., which agrees that HbA1c is a highly accepted predictor of diabetic complications. They validate its part in early stress of kidneys and systemic inflammation [19].

**GDF-15 and ARFIP2 comparison between patients with T2DM and controls.**

According to Figure 1, the median GDF-15 level in the control group would be larger than that in the T2DM group. This trend comes as a surprise since GDF-15 is normally increased in metabolic distress and cardiometabolic illness; higher values in the healthy controls suggest either a difference in samples/measures or confounding variables instead of a direct biological impact.

Figure 2 indicates that the ARFIP2 levels among T2DM are numerically less than among controls. This trend is biologically feasible because ARFIP2 is involved in insulin-relating actin remodeling and vesicular traffic.

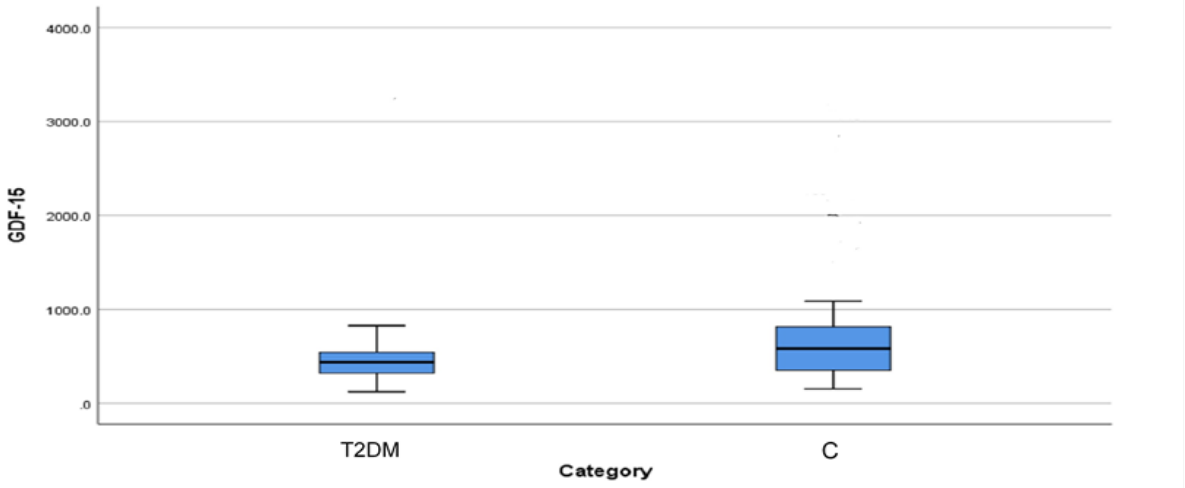


**Figure 1.** Differences in GDF-15 between T2DM patients and control.

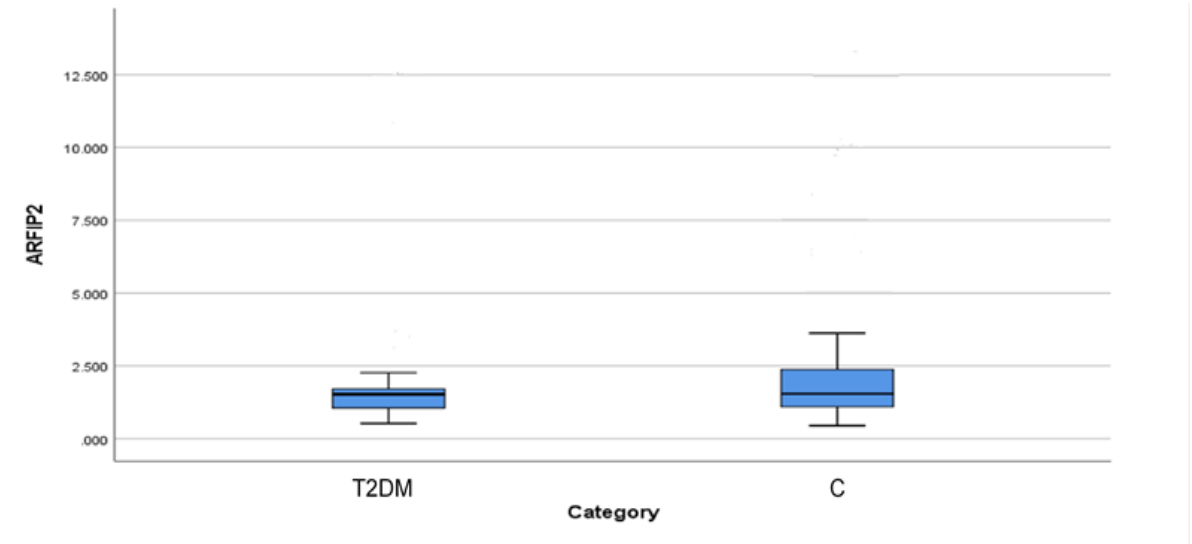


**Figure 2.** Differences in ARFIP2 between T2DM patients and controls.

Some of the earlier research concurrent with the present research and indicate that metformin elevates the circulating GDF15 and mediates the effects of appetite/weight through the glial cell-derived neurotrophic factor receptor alpha-like) pathway (GFRAL), confirming that there is strong medication effect on GDF15. In case your T2DM group was not adequately exposed to metformin or had other confounding agents that inhibit GDF -15, reduced concentrations in T2DM are likely. They generalize context-specific GDF-15 control by mitochondrial stress, inflammation, and therapeutic therapies and propose heterogeneity in metabolic phenotypes and role of comorbidities and renal dysfunction [20], [21].

While other studies show higher circulating GDF-15 in diabetes versus controls, consistent with its role as a stress biomarker in metabolic disease. Current results diverge from this overall pattern. These studies associate higher GDF-15 with reduced eGFR, albuminuria, and adverse renal/cardiovascular outcomes in T2DM, reinforcing that typical T2DM populations especially with complications have elevated GDF-15 [22], [23].

**Comparison of routine parameters between male and female in T2DM patients' groups:**

Across adults with T2DM, males (n=33) and females (n=18) show closely similar values for fasting blood sugar (FBS), fasting insulin, HOMA-IR, and HbA1c. All between-sex comparisons are statistically non-significant p value, with slightly higher median HbA1c in females but overlapping ranges, Table 3.

**Table 3.** Comparison of FBS, Insulin, HOMA-IR and HbA1c between male and female in T2DM patients' groups.

***Mann Whitney U Test**

| Variables | Sex | | | | P. value* |
|---|---|---|---|---|---|
| | Male (n=33) T2DM | | Female (n=18) T2DM | | |
| | Mean± SD | Median Max -Min | Mean± SD | Median Max - Min | |
| **FBS (mg/dl)** | 221.91±55.263 | 200.00 (160-400) | 212.39±37.191 | 202.00 (150-280) | 0.929 |
| **Insulin (µlU/ml)** | 16.15±3.691 | 16.300 (9.2-26.1) | 16.21±3.1799 | 15.900 (11.1-22.1) | 0.898 |
| **HOMA-IR** | 8.882±3.430 | 8.700 (3.6-17.8) | 8.528±2.578 | 8.150 (5.4-14.1) | 0.813 |
| **HbA1c (%)** | 8.991±1.997 | 8.600 (5.4-14.5) | 9.772±2.714 | 9.950 (5.6-13.8) | 0.319 |

At 2024 a previous study reported that sex-related differences in glucose and insulin are partly mediated by iron status adjusting for iron indices attenuates the sex

association. This supports the current finding of non-significant between-sex differences in common glycemic and insulin-resistance markers [24].

Larsen et al. study agrees with current results that emphasizes personalized tissue-level heterogeneity in insulin resistance that often exceeds sex-based group differences in standard clinical metrics [25].

Whereas some studies found sex differences in how metabolic inflammation and insulin resistance relate to incident T2DM, implying potential sex-specific pathophysiology that may manifest as different glycemic trajectories or control patterns in some populations. They suggested that in larger or differently composed cohorts (e.g., prediabetes, untreated, or with distinct adiposity/inflammation profiles), sex differences can be detectable particularly when focusing on upstream risk pathways rather than cross-sectional treated T2DM metrics [26], [27].

**Comparison of GDF-15 and ARFIP2 between male and female in T2DM patients' groups**:

The mean GDF-15 appears higher in females with T2DM than males, but variability is extreme in females and the sex comparison is not statistically significant (p= 0.821). This suggests no detectable sex-based difference in circulating GDF-15 within this sample, likely constrained by sample size and high dispersion.

The mean ARFIP2 is numerically higher in females, again with wide variability and the sex comparison is not significant (p= 0.672), Table 4.

**Table 4.** Comparison of GDF-15 and ARFIP2 between male and female in T2DM patients' groups,

| Variables | Sex | | | | P. value* |
|---|---|---|---|---|---|
| | Male (n=33) T2DM | | Female (n=18) T2DM | | |
| | Mean± SD | Median Max -Min | Mean± SD | Median Max -Min | |
| **GDF-15** | 429.2±155.01 | 437.4 (119.9-825.8) | 571.3±667.38 | 439.15 (186.9-3183.0) | 0.821 |
| **ARFIP2** | 1.437±0.5129 | 1.555 (0.524-3.175) | 2.394±3.348 | 1.222 (0.532-12.33) | 0.672 |

***Mann Whitney U Test**

At 2025 a study underscores GDF-15's association with diabetes and obesity burden without establishing consistent sex-specific differences as a primary driver; elevations track metabolic stress across patients [28].

Likewise, a study at 2025 frames GDF-15 as an emerging biomarker whose levels reflect treatment and disease states, emphasizing context over inherent sex differences [29].

In some previous studies show that ARFIP2 is involved in membrane trafficking and actin cytoskeleton dynamics, processes relevant to insulin signaling and glucose metabolism. Sex differences in metabolic gene regulation are well-documented across

tissues, but they are not universal for every gene. The absence of a significant difference in those studies that align with current study may reflect tissue-specificity, cell-type expression, or assay variability rather than the absence of any biological sex effect [30], [31].

Previous study demonstrated pervasive sex differences in gene expression networks, implying that metabolic and stress-response pathways can be sexually dimorphic and, in principle, could include regulators like ARFIP2 or upstream factors affecting GDF-15 [30].

Also, a previous study that disagree with current results indicate T2DM can exert greater adverse mortality effects in females, suggesting downstream pathophysiology may be sex-modulated. Even if circulating GDF-15 levels are similar, the clinical consequences of equivalent biomarker levels could differ by sex due to divergent risk profiles and hormonal milieu [32].

GDF-15's biology is tied to integrated stress responses (e.g., mitochondrial stress, inflammation). These pathways are activated by cardiometabolic load and renal dysfunction common to both sexes with T2DM. Contemporary analyses stress that medication effects and comorbidity burden dominate GDF-15 variability, diluting simple sex contrasts in small cohorts [22].

Sex hormones (estrogen and androgens) and sex-chromosome effects shape immune-metabolic signaling, adipose biology, and hepatic pathways. Systems-level transcriptomics reveal sex-divergent regulatory networks that could modulate proteins like ARFIP2 and cytokines indirectly, producing sex differences that require larger, stratified samples and multi-omics control to detect [32].

**Correlation among parameters included study of T2DM and control groups**

**A. Correlation among parameters included study of T2DM**

As shown in table 5 proportional correlation between HbA1c, FBS, Insulin and HOMA-IR (P =0.0001) respectively, while the same table reveals an inverse statistically significant correlation between HbA1c and BMI (P=0.0001) in T2DM. Furthermore, there is a proportional direct, significant, and strong correlation between HOMA-IR with FBS and Insulin at (P=0.0001) for each other. However, the data of the T2DM was appear that there is a proportional direct correlation between FBS and Insulin (P=0.004). While there is an inverse statistically significant correlation between HbA1c and BMI (P=0.027).

**Table 5.** Correlation among parameters included study of T2DM.

| Category | | | BMI (kg/m2) | FBS (mg/dl) | Insulin(µIU) | HOMA-IR | HbA1c (%) | GDF-15 | ARFIP2 |
|---|---|---|---|---|---|---|---|---|---|
| T2DM | Age (years) | R | 0.101 | -0.141 | -0.232 | -0.212 | -0.147 | 0.106 | -0.129 |
| | | Sig | 0.479 | 0.323 | 0.102 | 0.135 | 0.304 | 0.457 | 0.368 |
| | BMI | R | | -0.255 | -0.086 | -0.201 | -309 | -0.012 | -0.155 |
| | (kg/m²) | Sig | | 0.071 | 0.549 | 0.157 | 0.027 | 0.934 | 0.278 |
| | FBS | R | | | 0.395 | 0.777 | 0.677 | 0.087 | 0.039 |
| | (mg/dl) | Sig | | | 0.004 | 0.0001 | 0.0001 | 0.542 | 0.785 |
| | Insulin(µIU) | R | | | | 0.852 | 0.370 | 0.265 | 0.060 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Sig | | | 0.0001 | 0.008 | 0.060 | 0.994 |
| HOMA-IR | R | | | | 0.520 | 0.238 | 0.057 |
| | Sig | | | | 0.0001 | 0.092 | 0.690 |
| HbA1c (%) | R | | | | | 0.109 | 0.101 |
| | Sig | | | | | 0.447 | 0.483 |
| GDF-15 | R | | | | | | 0.226 |
| | Sig | | | | | | 0.110 |

**Spearmen test**

Previous studies show direct effects on metabolic signaling pathways and glucose transporter trafficking, consistent with ARFIP2's stronger associations with acute insulin resistance indices compared with renal filtration markers. ARFIP2 is broadly expressed with functional roles in intracellular trafficking aligning with weaker renal correlations. Insulin signaling depends on proper endosomal sorting and receptor trafficking; ARFIP2's function sits upstream of the phenotypes captured by fasting insulin/HOMA-IR, making those correlations biologically plausible, while renal function indices are less directly tied to ARFIP2's core role [33], [34].

Several unbiased proteomic studies of insulin resistance and glycemic control highlight secreted cytokines, complement factors, and liver-derived proteins, ARFIP2 does not consistently emerge as a circulating marker of insulin resistance. If ARFIP2 is largely intracellular, circulating measurements may be assay-dependent, low-abundance, and variable, reducing reproducibility across studies. Differences in comorbidity, therapy, sample handling, and analytical platforms can produce or obscure correlations. That not align with current study [13], [35].

**B. Correlation among parameters included study of control**

Data of present study was showed direct proportional significant correlation between FBS with BMI (P=0.002), Insulin with BMI(P=0.0001), HOMA-IR with BMI, FBS and Insulin (P=0.0001, P=0.002) respectively, HbA1c with BMI, FBS, Insulin and HOMA-IR (P=0.044, P=0.002, P=0.001) and P=0.0001 respectively.

**Table 6.** Correlation among parameters included study of control.

| Category | | | BMI (kg/m2) | FBS (mg/dl) | Insulin(µIU) | HOMA-IR | HbA1c (%) | GDF-15 | ARFIP2 |
|---|---|---|---|---|---|---|---|---|---|
| control | Age (years) | R | 0.053 | 0.033 | -0.190 | **0.146-** | **0.074** | **0.198** | **0.058** |
| | | Sig | 0.690 | 0.800 | 0.146 | **0.266** | **0.572** | **0.130** | **0.661** |
| | BMI (kg/m²) | R | | **396**0. | **507**0. | **557**0. | **261**0. | **0.008** | **0.063-** |
| | | Sig | | **0.002** | **0.0001** | **0.0001** | **0.044** | **0.954** | **0.612** |
| | FBS (mg/dl) | R | | | **0.204** | 0.392 | **388**0. | **0.017** | **0.123** |
| | | Sig | | | **0,117** | 0.002 | **0.002** | **0.898** | **0.348** |
| | Insulin(µIU) | R | | | | **963**0. | **429**0. | **0.044** | **0.033** |
| | | Sig | | | | **0.0001** | **0.001** | **0.740** | **0.801** |

| | | | | |
|---|---|---|---|---|
| **HOMA -IR** | **R** | **457**0. | **0.052** | **0.070** |
| | **Sig** | **0.0001** | **0.691** | **0.597** |
| **HbA1c (%)** | **R** | | **0.048** | **0.105** |
| | **Sig** | | **0.714** | **0.425** |
| **GDF-15** | **R** | | | **444**0. |
| | **Sig** | | | **0.0001** |

**Spearmen test**

Some previous studies showed that levels of GDF-15 were significantly elevated in obese and diabetic individuals, correlating with insulin resistance and BMI. GDF-15 is increasingly recognized as a biomarker of insulin resistance, obesity, and type 2 diabetes. Elevated GDF-15 correlates with higher HbA1c and HOMA-IR, consistent with the current findings. The negative correlation between ARFIP2 and GFR aligns with evidence that metabolic stress pathways accelerate renal decline. GDF-15 is secreted under mitochondrial and metabolic stress, explaining its correlation with HbA1c, insulin, and HOMA-IR. ARFIP2 may indirectly influence insulin signaling through cytoskeletal regulation of vesicle trafficking, affecting glucose uptake [28], [36].

On the other hand, some studies suggest GDF-15 may act as a protective metabolic messenger, reducing appetite and improving energy expenditure, which could mitigate insulin resistance rather than worsen it. While ARFIP2 correlations are significant here, its mechanistic role in glucose metabolism and renal function remains unclear. Some studies emphasize that ARFIP2 is more involved in actin cytoskeleton regulation and vesicular trafficking, not directly in metabolic pathways. Disagreement reasons may be that GDF-15's dual role; while elevated levels correlate with metabolic dysfunction, it may also represent a compensatory mechanism to reduce food intake and improve energy balance. ARFIP2's correlations may be secondary associations rather than causal, reflecting systemic metabolic stress rather than direct molecular involvement [37], [38].

**Limitation**

The same population contained 51 DM patients and 60 control participants; nevertheless, larger sample sizes may improve the reliability of the results. The study's approach was cross-sectional, and longitudinal research on patients over time can provide a deeper knowledge of disease processes and the impact of therapies. Even though GDF-15 and ARFIP2 levels have been linked to DM, no direct causal association can be proven from them. Age, menopausal status, BMI, and other medical conditions can all have an impact on these concentrations. The study's findings must be validated in an independent cohort to confirm their repeatability and generalizability.

## CONCLUSION

**Fundamental Finding:** The results indicate that gender does not significantly influence the distribution of T2DM in this study population, and this analysis suggests

that ARFIP2 is significantly associated with markers of insulin resistance and glycemic dysregulation in T2DM patients, while BMI and insulin resistance remain the dominant predictors of metabolic health in controls. **Implication :** These parameters not only reflect disease severity but also provide a strong foundation for exploring additional biomarkers such as GDF-15 and ARFIP2, particularly in the context of gender-based differences, and these findings support the hypothesis that ARFIP2 and GDF-15 gain greater relevance in diabetic conditions. **Limitation :** However, the observed male predominance among diabetic patients may warrant further exploration in larger cohorts to determine whether gender plays a subtle but clinically relevant role in T2DM susceptibility and progression. **Future Research :** Further exploration in larger cohorts is needed to determine whether gender plays a subtle but clinically relevant role in T2DM susceptibility and progression and to further investigate additional biomarkers such as GDF-15 and ARFIP2 in the context of gender-based differences.

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