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FN1 Levels as New Biochemical Marker for the Early Detection and Diagnosis of Infertility in Obesity Patients

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Abstract: ***Background and Aim:*** Obesity is the most prevalent metabolic disorder in industrialized nations. A common link between obesity and various other related disorders, including diabetes, insulin resistance, atherosclerosis, dyslipidemia, hypertension, inflammatory and cardiovascular disease. Fibronectin 1 (FN1) is a large extracellular glycoprotein located on the surface of animal cells and serves as the primary non-collagenous component of the extracellular matrix (ECM) and basement membrane. In the *present* -*study*, we aimed to assess serum levels of FN1 in obesity individuals and to – *evaluate* associations with the biochemical markers. ***Materials and Methods:*** The *study* was involving <120> Iraqi participants, comprising <60> obesity patients (<15>males / <45> females), their ages ranged from <25-55> years and <60>healthy control (<15>males / <45>females), their ages ranged from <25-55> years. Serum levels of FN1 and various demographic, anthropometric and biochemical parameters including age, gender, BMI; W/H; SBP; DBP; TNF-α; *T-CHO*; *HDL-C*; *TG*; *LDL-C*; *VLDL-C* and FSH were *measured* in all subjects. To compare the two groups and correlations evaluation among the investigated parameters was performed the statistical analyses. ***Results:*** The comparison between obesity and control groups respectively by the mean of the anthropometric and biochemical parameters levels that showed a significantly increased in BMI (30±2 versus 21±1, P=0.04), W/H (1.5±0.09 versus 0.82±0.07, P=0.02), TNF-α (11±0.8 versus 4±0.3, P=0.04), FSH (12±1 versus 10±0.5, P=0.04) and FN1 (400±25 versus 300±20, P=0.03). FN1 showed a significant strong positive correlation with BMI; W/H; TNF-α; and FSH levels in obesity patients. ***Conclusions:*** A significant strong positive association of FN1 levels with BMI, W/H, TNF-α and FSH in patients with obesity. Therefore, FN1 levels may be used as an early diagnostic marker to identify infertility in obesity patients.

Keywords: Obesity, Fibronectin 1 (FN1), Infertility, Index of *Body* - *Mass* (BMI), *Ratio* of *Waist* – to - *Hip* (W/H), Factor of *Tumor* – *Necrosis* -alpha (TNF-α), Hormone* of *Follicle* - Stimulating (FSH), Cholesterol* of *Total (T-CHO).

Research Paper

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INTRODUCTION

Obesity is most prevalent metabolic disorder in industrialized nations. A common link between obesity and various other related disorders, including diabetes, insulin resistance, atherosclerosis, dyslipidemia, hypertension, inflammatory and cardiovascular disease [1]. Although the association between obesity and dyslipidemia has been recognized for some time, the precise molecular mechanisms underlying this relationship remain poorly understood [2].

One molecule of interest is factor of tumor-necrosis-alpha (TNF-α), a cytokine that multifunctional; is primarily produced by macrophages, though it can also be secreted by other cell types [3]. Beyond its established role-in-host-defense, TNF-α also significantly elevated with expression levels observed in various rodent models of obesity [5]. The proposed key mediator TNF-α has been linking obesity to insulin resistance, due to its ability to interfere with insulin signaling pathways [6]. The crucial role of increased TNF-α production in fat tissue of mediating peripheral insulin resistance in obese rodents [7]. Importantly, neutralizing TNF-α in these insulin-resistant animals leads to marked improvements in peripheral insulin sensitivity [8].

Research on TNF-α – induced insulin resistance in both whole organisms and cultured cells has shown that TNF-α contributes to insulin resistance, at least partly, by intracellular signaling inhibiting from the receptors of insulin [9]. Importantly, this inhibitory effect can be reversed through the neutralization of TNF-α in vivo. Recent studies further highlight that impaired signaling through the insulin receptor is a key factor contributing to insulin resistance associated with obesity, a phenomenon observed in both human subjects and animal models [10].

The levels of TNF-α; are elevated significantly in the tissue of adipose for obese - individuals. Moreover, this increase strongly correlates with hyperinsulinemia a condition marked by elevated insulin levels despite normal blood glucose which serves as an indicator of insulin resistance [11].

Fibronectin 1 (FN1) is a large extracellular glycoprotein located on the surface of animal cells and serves as the primary non-collagenous component of the extracellular matrix (ECM) and basement membrane. The critical roles of FN1, a key member of the fibronectin family in various biological processes including wound healing, embryogenesis, blood clotting, immune defense, metastasis, as well as cell adhesion and migration during proliferation. Additionally, FN1 is implicated in fibrosis and several other pathological conditions [12].

The interaction between the multifunctional cytokine TNF-alpha and glycoprotein components of the ECM. We found that TNF-alpha binds strongly to fibronectin 1 (FN1) and laminin, with a weaker association observed with collagen. Certain cytokines of inflammatory and factors of growth that interact with components of glycosaminoglycan of the extracellular matrix (ECM). The primary site of binding for TNF-alpha on fibronectin was identified exhibiting a dissociation constant (Ki) in the range sub-nanomolar confirming the specificity of the interaction. These findings suggest that ECM glycoproteins like fibronectin can present cytokines such as TNF-alpha in a localized manner, modulating immune cell adhesion and potentially regulating their own cell-adhesive properties through interactions with cytokines [13-14].

TNF-alpha, an inflammatory cytokine primarily produced by macrophages and monocytes, interacts with fibronectin 1 (FN1), a key extracellular matrix protein. The TNF-alpha–fibronectin complex can modulate how cells engage with the extracellular matrix, potentially affecting tissue remodeling and immune responses. This interaction influences various processes of cellular such as cell adhesion and migration [15].

The high levels; from factor of tumor - necrosis - alpha (TNF-α) are; infertility - associated - with its in both women and men, potentially impacting oocyte quality, fertilization, sperm integrity, and endometrial receptivity. Elevated TNF-α can stem from conditions like endometriosis or polycystic ovary syndrome (PCOS), and specific gene variations are linked to increased infertility risk [16]. However, TNF-α is also a crucial immune factor for normal pregnancy, and a precise balance between pro-inflammatory and anti-inflammatory cytokines is necessary for successful implantation and outcomes [17].

In the evaluation of serum TNF-α levels in women with a history of infertility, cytokines; such as; factor of *tumor* – *necrosis* - alpha (TNF-α), which promote response of immunity, are believed* - to; *play* a role* not only in recurrent spontaneous abortions but also potentially in infertility. Suggesting that immune mechanisms may underlie certain forms of infertility. The findings also indicate that elevated serum TNF-α could serve as a potential biomarker for a subset of infertile women [18].

High TNF-alpha concentrations have been linked to disruptions in ovulation, fertilization, and implantation, contributing to infertility in some cases. While TNF-alpha does not directly cause infertility, elevated levels can adversely affect key reproductive processes. Accordingly, TNF-alpha inhibitors have been explored as treatments for infertility related to inflammatory conditions. TNF-alpha may also impair oocyte quality, which can negatively influence outcomes in assisted reproductive technologies (ART) [19]. Increased TNF-alpha levels, especially in follicular fluid, are associated with lower estradiol concentrations and reduced fertilization rates. Elevated TNF-alpha can create a hostile environment, potentially leading to pregnancy loss. TNF-alpha plays a significant role in implantation, placentation, and pregnancy maintenance by modulating the maternal-fetal interface [20].

This study aimed to assess serum levels of FN1 in obesity - individuals and to investigate - associations with the evaluated biochemical markers.

EXPERIMENTAL

Demographic evaluation for individuals and study design

The study were conducted with approvals from the regional ethical committee of University of Al-Qadisiyah, Faculty of Science. Informed consent forms were obtained from each participant before beginning the research. The design of this study was as two different groups included <120> subjects, <60> obesity patients (<15>males / <45>females), their ages ranged from <25-55> years. The register of patients* – were in “Diwaniya* – Teaching* - *Hospital” in *Al-Qadisiyah* – *Iraq*; throughout the period from June 2025 to August 2025. To compare the results; <60> healthy adults (<15>males / <45>females) were included as a control group, their ages ranged from <25-55> years.

Exclusion criteria

Individuals with serious uncontrolled chronic – diseases; (such as: stage of end for disease of renal, advanced disease of heart, active cancer, severe liver disease, or major endocrine disorders. Pregnant or breastfeeding women. Individuals who have recently undergone weight-loss surgery (such as sleeve gastrectomy or gastric bypass). Individuals taking medications that affect body weight (such as corticosteroids, antidepressants, thyroid medications, or appetite stimulants) and smokers or substance abusers, were also excluded.

Collection of samples

The collection of control and patients blood samples were between <8:30-10:00> a.m. after an overnight fast of <8–12> hours using <23> gauge needles through antecubital venipuncture, with <5> milliliters; of blood of venous that drawn – from - each participant. At temperature of room; the blood that collected was left to allow clot in plain tubes. Subsequently, the samples were centrifuged; then divided - into - five aliquots and stored for analysis in future.

Anthropometric evaluation

For the calculation of index of body mass (BMI), height was first converted from centimeters to meters. By *using the following* *formula*; BMI = weight (kg) / [height (m)]²; BMI was calculated. Additionally, by dividing circumference of waist by circumference of hip, as follows; WHR = circumference of waist (cm) / circumference of hip (cm); the ratio of waist – to – hip (W/H) was calculated [21].

Biochemical evaluation

By using a monitor of validated digital for blood pressure to measure (SBP) and (DBP); after the participant; seated – quietly – for<5> minutes, blood pressure was measured. Measurements were taken on the non-dominant arm (usually the left arm). Two separate readings were recorded with a 2-minute interval between them, and the average of the two readings was calculated. The serum level of (TNF-α) was quantified by using a commercial; ELISA - kit from CORTEZ (USA), employing an ELISA microplate washer and reader, in accordance with the enzyme-linked immunosorbent assay methodology. The (FSH) concentration was assessed through a spectrophotometric assay (Type 3) by using a kit provided by Monobind Inc. (USA). To determine the serum (FN1) levels, enzyme-linked immunosorbent assay kits from MELSIN (China) were utilized. The - determination of; (T-CHO), (TG), (HDL-C), (LDL-C) and (VLDL-C) concentrations by using a spectrophotometric kit from LiNEAR (Spain).

Bio-statistical analysis

SPSS software (version 24) with Microsoft - Excel 2010 were; used – to analyze the – collected - data. Comparative* statistical* tests*; were* – *conducted to *determine; significant* – *differences – *between* - the investigated groups. Additionally, analysis of Pearson’s correlation coefficient; was – employed – to – examine; potential associations - between-the studied parameters.

RESULTS

As illustrated in Table 1, the mean of age; gender; SBP; DBP; T-CHO; HDL-C; TG; LDL-C and VLDL-C demonstrated no significant variations between the obesity and the control groups. Nevertheless, the mean of BMI; W/H; TNF-α; FSH and FN1 levels *showed*; a significantly* increased* in the obesity group; as *compared* - *with the – *control - *group, these findings are depicted in Figure 1 (A, B, C, D, E).

Table 1: Demographic, anthropometric and biochemical data for the obesity and the control groups

Parameters	Groups		P-value
	Control Mean ±SD (n=60)	Obesity Mean ±SD (n=60)	
Age (year)	40±8	40±10	0.85
Gender Males/Females	15(25%)/45(75%)	15(25%)/45(75%)	0.97
BMI (kg/m2)	21±1	30±2	0.04
W/H	0.82±0.07	1.5±0.09	0.02
SBP (mmHg)	120±10	130±13	0.76
DBP (mmHg)	78±4	80±6	0.84
TNF-α (pg/mL)	4±0.3	11±0.8	0.04
T-CHO (mg/dL)	112±12	114±13	0.95
TG (mg/dL)	94±10	96±12	0.71

Parameters	**Groups**		**P-value**
	Control Mean ±SD (n=60)	**Obesity Mean ±SD (n=60)**	
HDL-C (mg/dL)	44±8	42±9	0.64
VLDL-C (mg/dL)	20±7	23±8	0.12
LDL-C (mg/dL)	59±10	60±13	0.23
FSH (IU/L)	10±0.5	12±1	0.04
FN1 (µg/mL)	300±20	400±25	0.03

Significance: A <p-value> of ≤ 0.05 - was *considered*- *significant*, *Data* - *represented* as Mean ± SD; SD: <*Deviation* -of *Stander*>, n: <*Number* - of - *subjects*>, BMI: <*Index* of *Body* - *Mass*>, W/H: <*Ratio* of *Waist* – to - *Hip*>, SBP: <*Blood* - *Pressure* of *Systolic*>, DBP: <*Blood* - *Pressure* of *Diastolic*>, TNF-α: <*Factor* of *Tumor* – *Necrosis* – alpha>, FSH: <*Hormone of *Follicle* - *Stimulating*>, T-CHO: <*Cholesterol* of *Total*>, TG: <*Triglyceride*>, HDL-C: *Cholesterol* of <*High – *Density> - *Lipoprotein*, LDL-C: *Cholesterol* of <*Low – Density*> - *Lipoprotein*, VLDL-C: *Cholesterol* of <*Very – *Low* – *Density*> - Lipoprotein*, FN1: Fibronectin 1.

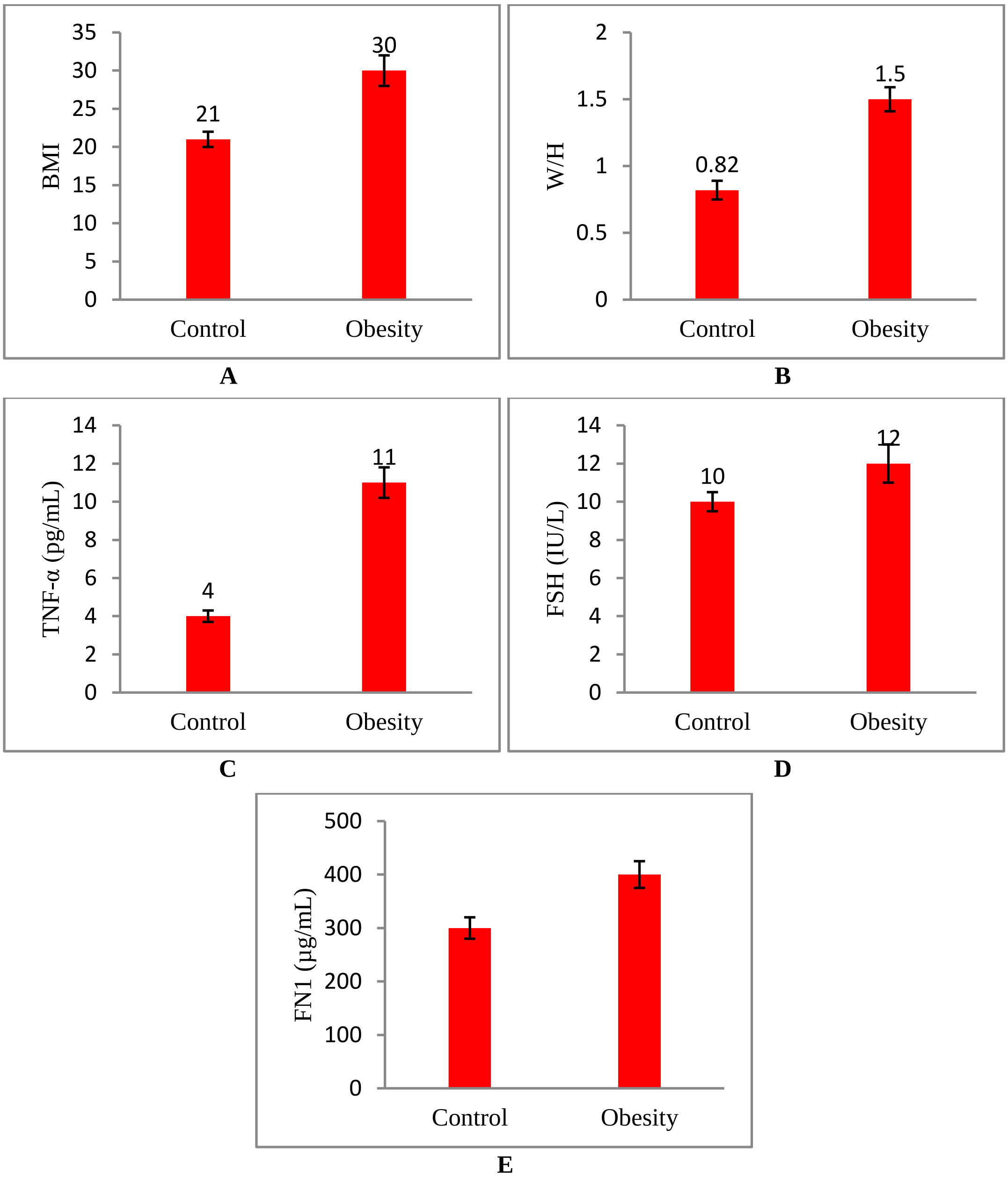


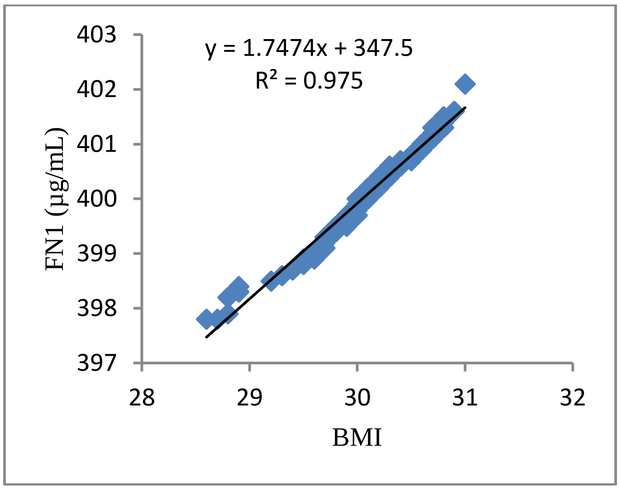
Figure 1: Comparison of serum A: BMI, B: W/H, C: TNF-α, D: FSH and E: FN1 levels between the obesity and control groups

As shown in Table 2, that displays the results of a linear regression analysis assessing the relationship between levels of serum FN1 concentrations and selected demographic, anthropometric and biochemical parameters in individuals with obesity. The findings revealed that no strong significant correlation between FN1 and other studied parameters, except that BMI, W/H, TNF-α and FSH levels showed a strong significant positive correlation with FN1 level, as shown in Figure 2 (A, B, C, D).

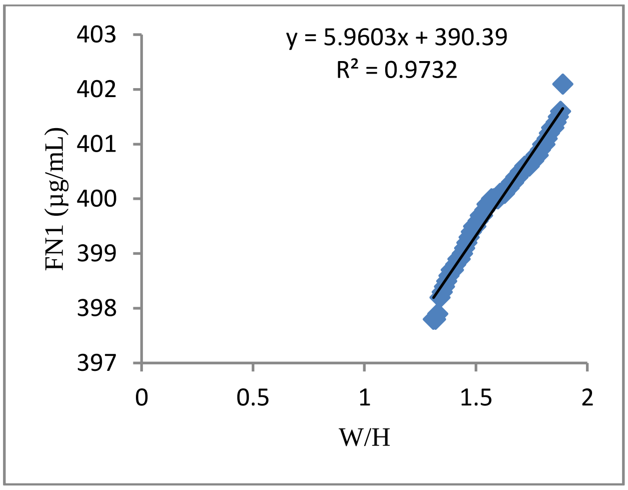
Table 2: Correlation between serum FN1 levels and others demographic, anthropometric and biochemical parameters in the obesity group

Parameters	FN1 (µg/mL)	
Age (year)	r	0.45
	P-value	0.93
BMI (Kg/m2)	r	0.98
	P-value	0.04
W/H	r	0.98
	P-value	0.03
SBP (mmHg)	r	0.15
	P-value	0.69
DBP (mmHg)	r	0.25
	P-value	0.83
TNF-α (pg/mL)	r	0.99
	P-value	0.01
T-CHO (mg/dL)	r	0.26
	P-value	0.45
TG (mg/dL)	r	0.43
	P-value	0.61
HDL-C (mg/dL)	r	0.12
	P-value	0.93
VLDL-C (mg/dL)	r	0.46
	P-value	0.79
LDL-C (mg/dL)	r	0.31
	P-value	0.58
FSH (IU/L)	r	0.99
	P-value	0.02

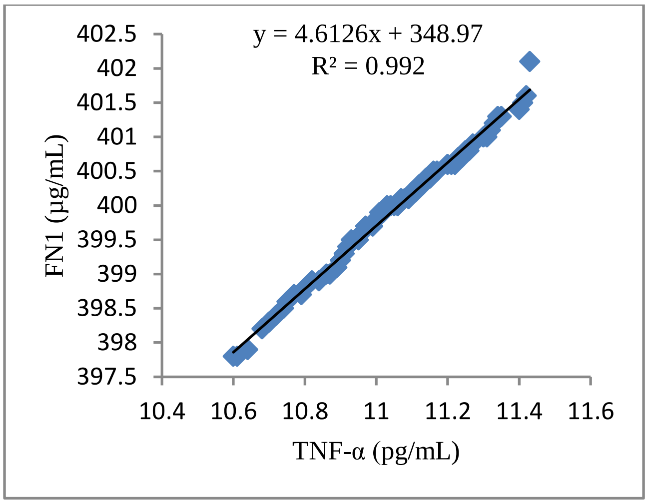
Significance: A <p-value> of ≤ 0.05 - was *considered*- *significant*, , r: *Person’s* – *correlation* *coefficient*, BMI: <*Index* of *Body* - *Mass*>, W/H: <*Ratio* of *Waist* – to - *Hip*>, SBP: <*Blood* - *Pressure* of *Systolic*>, DBP: <*Blood* - *Pressure* of *Diastolic*>, TNF-α: <*Factor* of *Tumor* – *Necrosis* – alpha>, FSH: <*Hormone of *Follicle* - *Stimulating*>, T-CHO: <*Cholesterol* of *Total*>, TG: <*Triglyceride*>, HDL-C: *Cholesterol* of <*High – *Density> - *Lipoprotein*, LDL-C: *Cholesterol* of <*Low – Density*> - *Lipoprotein*, VLDL-C: *Cholesterol* of <*Very – *Low* – *Density*> - Lipoprotein*, FN1: Fibronectin 1.



A



B



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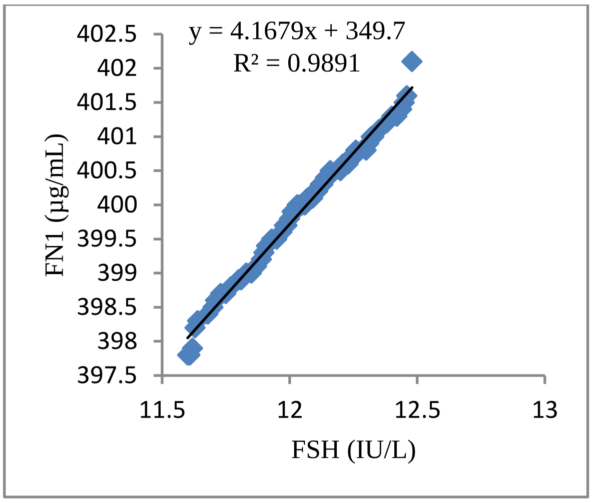

D

Figure 2: Correlation between serum FN1 levels and A: BMI, B: W/H, C: TNF-α and D: FSH in the obesity group

Table 3 presents the ROC curve analysis for FN1, revealing a cut-off point of 96.7% for detecting obesity patients. The – *area*; *under* – the - *curve* (AUC) *was* - *calculated* at 0.979, reflecting high diagnostic performance. FN1 demonstrated a sensitivity of 96.7% and a specificity of 100%, as shown in Figure 3.

Table 3: Receiver operating characteristic (ROC) and area under the curve (AUC) analysis of FN1 in diagnosing obesity patients

Variable	Group	Cut-off concentration %	Sensitivity %	Specificity%	AUC	Std. Error	95% CI of AUC	P-value
FN1	Obesity	96.7	96.7	100	0.979	0.015	0.949 -1.000	0.001

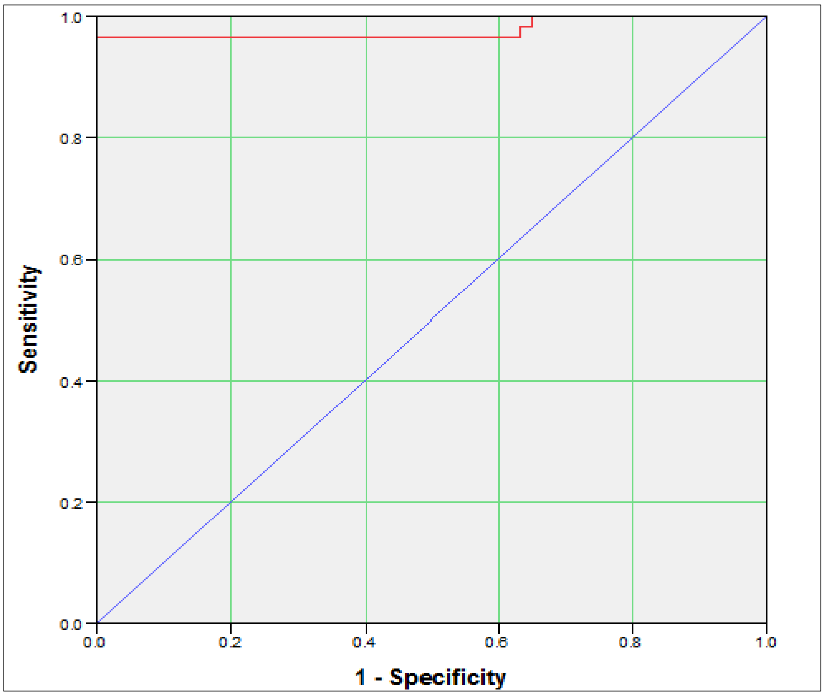

Figure 3: Receiver operating characteristic (ROC) curve analysis of FN1 in diagnosing obesity patients

DISCUSSION

The *present* study revealed a significantly increased in serum fibronectin 1 (FN1), BMI, W/H ratio, TNF-α and FSH levels among individuals with obesity. FN1 levels showed a significant strong positive correlation between with BMI, W/H, TNF-α and FSH levels in obesity patients. This pattern can be explained by the fact that obesity is a major clinical condition that associated; with - chronic inflammation in the low – grade that characterized by; the persistent elevation of inflammatory mediators such as TNF-α primarily secreted by visceral adipose tissue. These inflammatory cytokines have direct detrimental effects on reproductive function: they disrupt hormonal balance, impair of ovulation and maturation of follicular; in - females, and negatively affect for sperm – quality - and spermatogenesis; in - males. Additionally, they promote the-production – of – oxygen - species that reactive (ROS), leading - to- damage of DNA - in gametes, and stimulate fibrotic changes in reproductive tissues by activating the remodeling of the extracellular matrix (ECM). As part of this inflammatory response, the expression of fibronectin 1 (FN1) a major ECM glycoprotein is significantly upregulated, FN1 is initially produced as a protective response aimed at tissue repair. Therefore, FN1 can be regarded as a predictive biomarker that reflects the progression of infertility, particularly in obesity individuals.

The FN1 matrix is vital for organizing collagen networks. Tissue of fibrotic – is - marked by- the accumulation-of- abnormal proteins for matrix of extracellular (ECM). Among these, fibronectin 1 (FN1) facilitates interactions between various ECM components and cells, as well as supporting the assembly of other ECM elements [22]. When fibroblasts proliferate excessively, they can significantly impair lung function a hallmark of pulmonary fibrosis. Notably, FN1 expression is upregulated in lung fibroblasts and is implicated in TGF-β–driven differentiation into myofibroblasts [23]. Fibroblasts, particularly those in the lungs, are the primary producers of collagen, and their increased numbers have been associated with enhanced collagen deposition and the advancement of pulmonary fibrosis. This aligns with our findings, where FN1 expression was markedly elevated in mice with dexamethasone-induced pulmonary fibrosis, while silencing FN1 expression led to a substantial reduction in fibrosis markers [24].

Subsequent in vivo and molecular experiments confirmed that P. carinii infection leads to increased FN1 expression, which contributes to the development of pulmonary fibrosis accompanied by an inflammatory response [25]. In previous study, was identified a significant upregulation of FN1 in lung tissues from P. carinii-infected mice through differential expression analysis of mRNAs (DEmRNAs) [26]. Nonetheless, these offer important insights into the molecular pathways involved in the development of lung fibrosis. The exact regulatory mechanisms through which FN1 contributes to pulmonary fibrosis remain unidentified, and the downstream genes influenced by FN1 have not yet been experimentally validated [27].

The tumor microenvironment comprising the - matrix of the extracellular (ECM), hormones and cytokines play a role-in-regulating; various – biological - processes. In- squamous-cell; of head and neck - carcinoma (HNSCC), fibronectin (FN1), a major ECM protein surrounding tumor cells, has been shown to facilitate both migration and invasion [28]. Recent studies have emphasized the complex interactions among these components, especially the bidirectional communication with the ECM as cells invade and migrate through tissues during metastasis. FN1 enhances cell motility during tumor progression, and although multiple integrin receptors mediate cell adhesion to FN1, the integrin α5β1 is recognized as the primary receptor driving tumor cell invasion. Binding of α5β1 to FN1 is also essential for epithelial cell proliferation and role in regulating tumor angiogenesis [29].

Previous studies have reported that fibronectin 1 (FN1) and factor of tumor – necrosis - alpha (TNF-α) each play independent roles in promoting tumor progression. However, no direct evidence has been provided regarding a cooperative interaction between these two molecules [30].

In previous study, treatment of HN-22 cells with either FN1 or TNF-α alone did not alter OPN expression. They initially examined the impact of TNF-α and fibronectin 1 (FN1) on OPN expression in the HN-22 cell line. The treatment with varying concentrations of TNF-α alone did not alter OPN mRNA levels. However, FN1 was found to enhance the TNF-α–induced expression of OPN, a process mediated via β1 integrin and activation of the ERK signaling pathway. In contrast, RT-PCR analysis of T cells grown on FN1-coated plates indicated that TNF-α had no effect on OPN expression in this non-cancerous epithelial cell line. However, when HN-22 cells were cultured on FN1-coated plates, TNF-α significantly increased OPN mRNA and protein expression in a dose-dependent manner [31].

While previous studies have reported that TNF-α increases OPN expression in macrophages and biliary epithelial cells in the context of inflammation, no such evidence had been shown in tumor cells until now. They demonstrated for the first time that fibronectin 1 (FN1) can mediate the-effect-of- factor of – tumor - necrosis- alpha (TNF-α) on the regulation of osteopontin (OPN) expression in HN-22 cells [32]. The limited response of tumor cells to TNF-α under in vitro conditions may be due to the absence of integrative cues typically provided by the tumor microenvironment. For example, TNF-α alone lacks the pro-adhesive and chemotactic signals required to fully activate downstream pathways in cultured cells [33].

Previous studies indicated that TNF-α binds specifically to fibronectin 1 (FN1) and laminin, with weaker interactions observed with collagen. They examined the binding behavior of TNF-α, a multifunctional cytokine, to various ECM glycoproteins. Notably, radiolabeled TNF-α (^125I-TNF-α) remained bound to immobilized FN1 or FN-N′ for over 24 hours. This interaction not only preserves but spatially restricts TNF-α activity, thereby modulating immune cell adhesion and contributing to the regulation of ECM's cell-adhesive properties through. These findings suggest that FN1, a major ECM glycoprotein, may serve as a localized reservoir of functionally active TNF-α cytokine association [34].

CONCLUSION

This study was indicated that a significant strong positive association of FN1 levels with BMI, W/H ratio, TNF-α and FSH in patients with obesity. Therefore, in obesity patients; levels of FN1; as new biochemical marker; for–the early detection-and-diagnosis of infertility. It is *recommended* *that* *future* *studies* investigate the tissue-specific expression of fibronectin 1 (FN1), particularly in adipose tissue and endometrial cells. Understanding the primary sources of FN1 and its localized effects may help clarify its role in the pathophysiology of obesity. Such studies could reveal whether FN1 acts systemically or exerts direct paracrine or autocrine effects within organs.

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CONFLICT OF INTERESTS

There was no conflict of interest among the authors.

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