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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 glycoprotein serves as a component of the matrix. 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, this increase with hyperinsulinemia a condition involved elevated of insulin levels [11].

Fibronectin 1 (FN1) is a glycoprotein serves as a component of the matrix. 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. They 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 glycosaminoglycan. The primary site of binding for TNF-alpha on fibronectin was identified exhibiting a dissociation constant in the the specificity of the interaction [13-14].

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

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

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

High TNF-alpha concentrations to disruptions implantation, in some cases contributing to infertility have been linked in ovulation and fertilization. While cause infertility TNF-alpha does not directly, affect key reproductive elevated levels can adversely processes. As treatments for infertility related to inflammatory accordingly, explored TNF-alpha inhibitors have been conditions. TNF-alpha which can negatively may also impair oocyte quality, influence reproductive [19]. Estradiol concentrations especially in follicular fluid and reduced fertilization rates. Elevated TNF-alpha can increased TNF-alpha levels, are associated with lower create, potentially leading to pregnancy loss a hostile environment. 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). The (TNF-α) assay kit by CORTEZ according to ELISA. The (FSH) assay kit by Monobind Inc according to spectrophotometric. The (FN1) assay kit by MELSIN according to ELISA. The (T-CHO), (TG), (HDL-C), (LDL-C) and (VLDL-C) assay kits by LiNEAR according to spectrophotometric.

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
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.

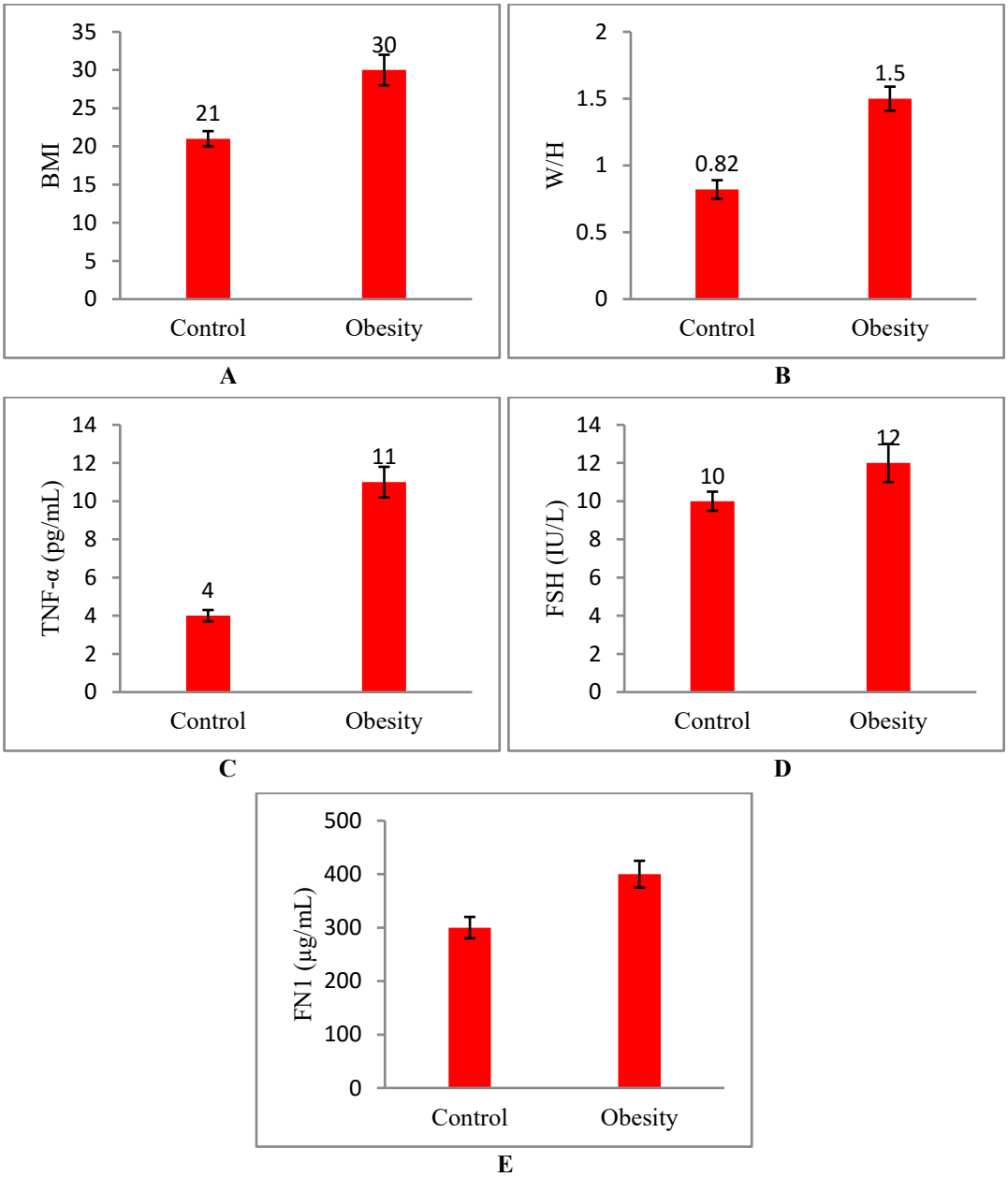

Figure 1: Comparison of serum A: BMI, B: W/H, C: TNF-α, D: FSH and E: FN1 levels between the obesity and control groups

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 P-value	0.45 0.93
BMI (Kg/m2)	r P-value	0.98 0.04
W/H	r P-value	0.98 0.03

SBP (mmHg)	r P-value	0.15 0.69
DBP (mmHg)	r P-value	0.25 0.83
TNF-α (pg/mL)	r P-value	0.99 0.01
T-CHO (mg/dL)	r P-value	0.26 0.45
TG (mg/dL)	r P-value	0.43 0.61
HDL-C (mg/dL)	r P-value	0.12 0.93
VLDL-C (mg/dL)	r P-value	0.46 0.79
LDL-C (mg/dL)	r P-value	0.31 0.58
FSH (IU/L)	r P-value	0.99 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.

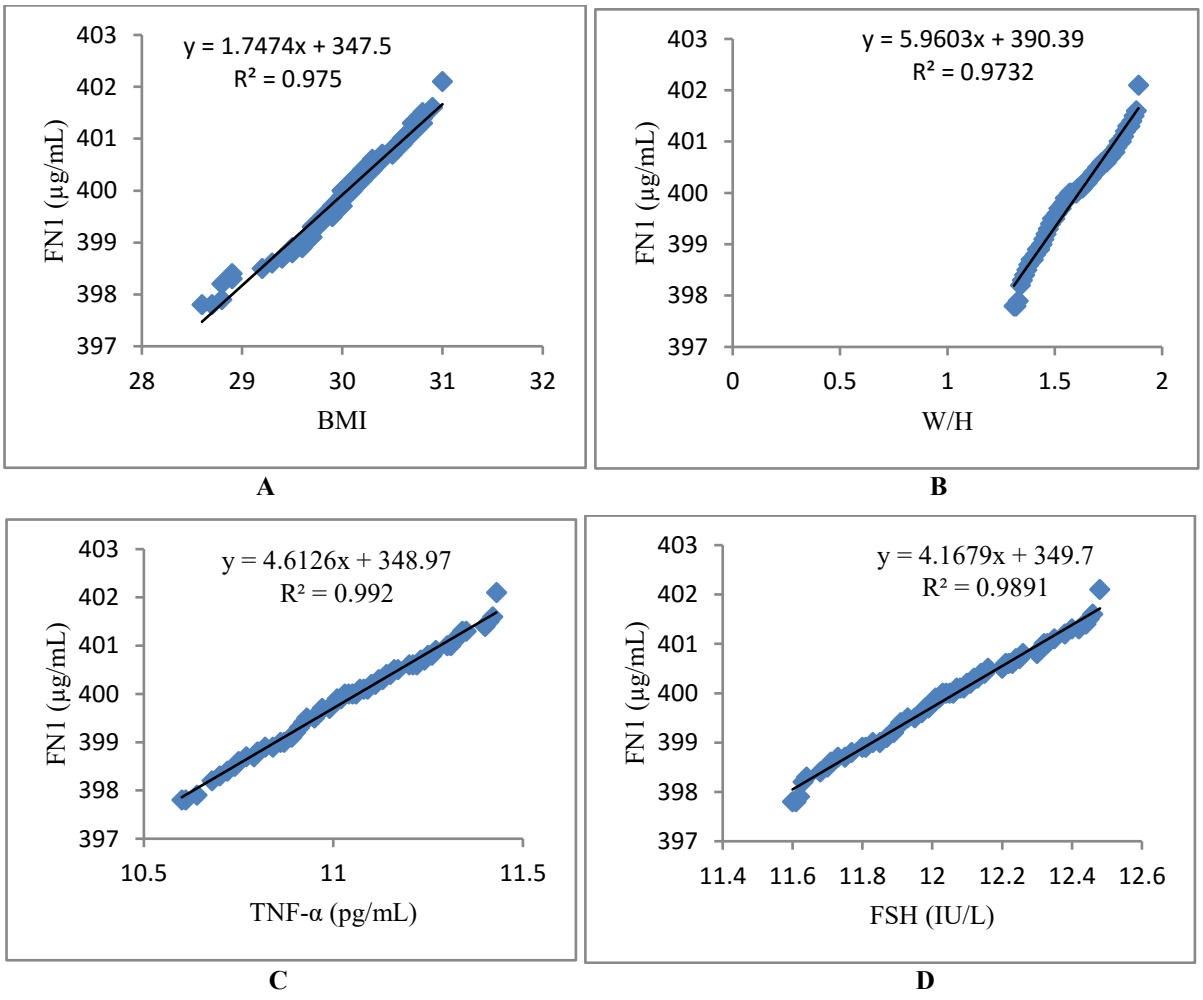

Figure 2: Correlation between serum FN1 levels and A: BMI, B: W/H, C: TNF-α and D: FSH in the obesity group

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

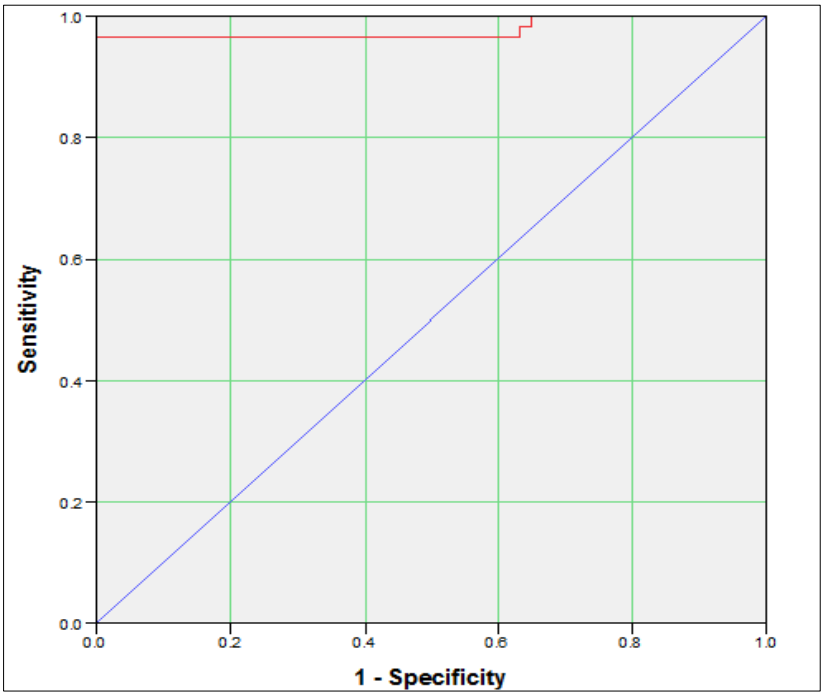

Figure 3: Receiver operating characteristic (ROC) curve analysis of FN1 in diagnosing obesity patients

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 the accumulation-of-abnormal proteins fibrotic – is - marked by-for matrix of extracellular. Among these, facilitates interactions cells, as well as of other elements supporting the assembly [22-23]. When fibroblasts proliferate excessively, between fibronectin 1 (FN1) various components and function a hallmark they can significantly impair lung of pulmonary fibrosis. Notably, upregulated FN1 into myofibroblasts TGF-β–driven differentiation [24-25]. Fibroblasts, are the primary producers of collagen, expression is in lung fibroblasts and is implicated in particularly those in the lungs, and their increased deposition and of pulmonary fibrosis the advancement. This aligns with our findings, was markedly elevated numbers have been associated with enhanced collagen where FN1 expression in mice with dexamethasone- expression led to in fibrosis

markers a substantial reduction induced pulmonary fibrosis, while silencing FN1 [26-27].

Subsequent and molecular experiments in vivo infection leads, development of pulmonary which contributes to the fibrosis accompanied by an confirmed, to increased FN1 expression carinii inflammatory response [28]. In previous study, of FN1 upregulation, carinii-infected expression analysis of mRNAs mice through differential [29]. Nonetheless, in lung tissues from was identified a significant these into the molecular pathways involved offer important insights in the development of lung fibrosis. The through which FN1 exact regulatory mechanisms contributes to pulmonary fibrosis remain unidentified, have not yet been experimentally validated [30-31].

The tumor the - matrix of the microenvironment comprising extracellular, hormones and cytokines various – biological - processes play a role-in-regulating;. In- squamous-cell; of head and neck - carcinoma, fibronectin (FN1), a major protein, has been shown to facilitate surrounding tumor cells both migration and invasion [32]. Recent studies have interactions among these emphasized the complex components, especially the bidirectional cells invade and migrate communication with the through tissues during metastasis. FN1 enhances cell motility during tumor progression, integrin receptors mediate and although multiple cell adhesion to FN1, the integrin is recognized as the primary receptor invasion driving tumor cell. Binding to FN1 is also essential for epithelial cell proliferation and role in regulating tumor angiogenesis [33-34].

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 [35].

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 [36]. 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 [37-38].

While previous studies have reported that TNF-α increases osteopontin (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 (OPN) expression in HN-22 cells [39-40].

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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