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RESEARCH ARTICLE

The level of fibroblast growth factor-2 prepared from Advanced Platelet Rich Fibrin (A-PRF) in obese Saudi subjects compared to healthy subjects

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Keywords

Fibroblast growth factor • Obesity • Periodontitis • Platelet Rich Fibrin

Summary

Background. *The prevalence of obesity has increased substantially in the last few decades. World Health Organization (2020) estimated that around 600 million obese adults worldwide were obese, and a further increase is expected in the future due to increased consumption of high-calorie diets and a sedentary lifestyle as per the evidence.*
Aim. *To evaluate and compare the level of fibroblast growth factor platelet rich fibrin (A-PRF) in obese subject compare to healthy weight subject.*
Methods. *Blood samples were collected from 23 volunteers, 15 obese subject (test group) and 8 non-obese (control group) at Riyadh Elm University. Considering the smaller sample size of our study, the results are to cautiously be interpreted for generalizability. Studies employing larger sample size are recommended to overcome this point. But considering the meticulous study procedure adhering to the study protocol and set criteria, the study pronounces greater internal validity in the sample chosen. The medical, dental histories, an interview and clinical examination was performed to check the eligibility of the participants to be involved in this study, Blood sample was collected in 10 ml syringe, then being processed using A-PRF centrifugation protocols. Ten milliliters of whole blood without anticoagulant was centrifuged at 1,300 rpm for 14 minutes.*
Results. *The level of FGF-2 released from (A-PRF) concentration was significantly lower on obese which was measured on 4 different times (day 1, day 7, day 14 and day 28), compared to healthy.*
Conclusions. *There was decrease in FGF-2 level released from (A-PRF) from obese compared to healthy.*

Introduction

Periodontal regeneration is challenging and yet interesting arena of treatment strategy for the periodontitis [1]. Multiple cells and cell signaling cascades involved in the treatment of periodontal regeneration makes it still as a better treatment modality, where results and clinical outcomes are difficult to predict. However, challenge of periodontal regeneration is being addressed part by part and results are promising with available array of multiple treatment modalities [2, 3].
One of the well dealt regeneration strategies commonly utilized in the field of periodontics is the use of platelet concentrate [4]. Last decade has seen a tremendous growth in the platelet concentrate, with several modifications. First generation platelet concentrate Plate Rich Plasma (PRP), was popular and remained in this field for few years, with natural phenomena to change with better understanding of the methods and concepts, which gave the way to the development of second generation concentrate Platelet Rich Fibrin (PRF) [5, 6]. Platelet rich fibrin a modification of platelet concentrate is a boon to the periodontal regeneration has seen various applications in the field of dentistry. Its simplicity and chair side technique attracted naturally many periodontist, oral surgeons, dermatologists, orthopaedics professionalsand others in the field of medicine and dentistry with open hands. Several changes in the methodology in terms of speed and material used resulted in the development of newer PRF techniques with superior results in terms of regeneration. However there is definite variation in the final outcome or clinical results when PRF is used for the regeneration, which made the researchers to search for the factors affecting the same [7, 8]. With the methodological factors and materials used, impacting the clinical result, there are systemic factors may also contribute to the regenerative capability of PRF.
The first report on the relationship between obesity and periodontal disease appeared in 1977, when Perlstein et al. observed histopathologic changes in the periodontium of hereditary obese Zucker rats (Zucker and Zucker, 1962; Perlstein and Bissada, 1977). Using ligature induced periodontitis; they found alveolar bone resorption to be greater in obese animals compared with non-obese rats (Perlstein and Bissada, 1977).
The role of obesity in periodontal disease progression is interesting and manifolds [9]. In humans, systemic diseases have always been considered as a risk factor for the periodontitis. Obesity is a major independent risk factor for hypertension, coronary heart disease, osteoarthritis, and, in particular, type 2 diabetes. Among

the commonly associated systemic disease diabetes and obesity are taking the front row, which has been shown to alter the periodontal disease progression and clinical outcome in many evidence-based studies. The presence of periodontal disease in a diabetic individual is a serious health hazard. Based on few studies done, there appears to be stronger obesity-periodontitis association in women, non-smokers, and younger individuals than in the general adult population [1].

Obesity has impact on the host cells and molecular signaling. PRF, derived from the platelets is a host of several growth factors. Growth factors which are the key component of initial and later stages of healing process are released by several hematopoietic cells, including platelets. Growth factors always function in an order or in a cycle with the help of other growth factors and cytokines. Functioning of many inflammatory cells are expected to change the obesity, platelet derived growth factors are not immune to this [10].

Thus, the present study is expected to explore the PRF derived growth factors in obese patients compare to non-obese patients, so that the outcome of the study is utilized in the regenerative strategy to be employed in the obese patients.

Methods

This was a descriptive, cross sectional study conducted on 23 subjects, chosen randomly from post-graduate residents in dentistry programs at Riyadh Elm University. For this, both the medical and dental histories were retrieved with an interview and clinical examination, which was performed to check the eligibility of the participants. For randomization, an electronic mail was sent to all residents with a detailed explanation of the procedure asking them to respond in case if they are willing to volunteer for the study. They were asked to get the Body Mass Index (BMI) done, and it should be above 30 (obese). After that, the positive responses were matched with the study criteria to determine the group of the participants that we can take our final sample from. Each of matched responses was given a number. The final sample was chosen from the sorted group. One trained person extracted the blood from all participants who was not a part of the research team but involved for the expertise skill that performed the centrifugation process for all samples. Ethical approval was obtained from research committee in Riyadh Elm University with registration number FPGRP/43831005/340.

Preparation of PRF

Blood samples were collected from our volunteers, (23 total samples). 15 obese (test group) and 8 normal weight (control group). Blood was extracted by 10 ml syringe, which was then processed using A-PRF centrifugation protocols. Ten milliliters of whole blood without anticoagulant was centrifuged at 2,700 rpm (708 g) for 12 minutes, the fibrin clots were collected after centrifuging from the top of the centrifuge tubes. The PRF clots was placed into prepared dishes. For each sample, 5 ml of culture medium was added. Dulbecco's modified eagle medium (DMEM) was used for this purpose. We used PRF kit and tubes provided by PROCESS for PRF Company in France with U.S. FDA registration number 3007006186. The centrifuge machine used is HERMLE Z 206 A. This machine manufactured by HERMLE Labortichnik GmbH, Wehingen-Germany.

Protein Quantification with Enzyme-Linked Immunosorbent Assay (ELISA)

Principle of the assay

The kit is based on sandwich enzyme-linked immunosorbent assay technology. An antibody specific to FGF2 is pre-coated on to a 96-well plate. The standards and samples are added to the wells, incubated and washed with wash buffer. A biotin conjugated antibody specific to FGF2 is used for detection. TMB substrate is used to visualize HRP activity. TMB is catalyzed by HRP to produce a blue color product that changes into yellow after adding stop solution. The intensity of yellow is proportional to the FGF2 amount bound on the plate and then the concentration of FGF2 can be calculated.

To determine the amount of growth factors released from PRF at one day, seven days, 14 days, 28 days, samples will be kept at 37 C to allow for growth factor release. Protein quantification was carried out using ELISA machine. At desired time points, FGF-2 was quantified using an ELISA kit according to manufacturer protocol. Absorbance measured at 450 and 570 nm using a micro plate reader and the measurement at 570 nm were subtracted from the reading at 450 nm. Also, all samples were measured in duplicate.

Statistical analysis

Data analyses were carried out using Statistical Packages for Social Sciences (SPSS) version 21 (SPSS, Chicago, IL, USA). Descriptive statistics of FGF2 experiments were summarized using mean and standard deviation or median (range) whenever appropriate. Normality of test was also conducted using Kolmogorov-Smirnov and Shapiro Wilk test, p-value < 0.05 were considered as non-parametric. Correlation procedure had also been conducted using Pearson correlation. The statistical association of mean FGF-2 measured over time among obese and non-obese was conducted using independent t-test. Paired t-tests were also conducted to measure the mean differences among FGF-2 measured over time between each group (obese and non-obese). A p-value < 0.05 was considered statistically significant and a p-value < 0.01 was considered highly statistically significant.

Reliability analysis

Interclass Correlation Coefficient (ICC) was applied to determine the internal consistency of the study data. Based on the results the reliability analysis measured among four items (FGF-2 day to day 28) was 0.814 or 81.4% which indicates a very good internal consistency.

Results

We collected blood samples from 23 volunteers at Riyadh Elm University, 15 of them were classified into obese group (test group) and 8 participants were non-obese (control group). Table I presented the comparison between mean FGF-2 measured over time among obese and non-obese. It was found that, compared to non-obese patients, the level of FGF-2 measurement was significantly lower on obese which was measured on 4 different occasions (day 1 to day 28) ($p < 0.05$; 95% CI). The outcome indicated that the lower FGF2 concentration was associated with obese patients whereas higher FGF-2 concentration was associated with the normal group (non-obese).

Figure 1 depicted the distribution of mean FGF-2 which was measured in 4 different times (day 1, day 7, day 14 and day 28) between obese and non-obese. It can be shown that FGF-2 measurement among 4 different occasions were significantly lower in obese patients ($p < 0.05$).

Figure 2 depicted the trend line of FGF-2 which was measured in different times. As revealed, the mean FGF-2 measurement of non-obese was significantly lower at day 1 (mean 2.55) while day 28 was significantly higher (mean 2.74). In obese group, mean FGF-2 was

Tab. I. Comparison between obese and non-obese according to the mean FGF2 measured overtime (n = 23).

Factor	FGF2 measurement			
	Day 1 Mean ± SD	Day7 Mean ± SD	Day 14 Mean ± SD	Day 28 Mean ± SD
Study group				
Obese	1.46 ± 0.52	1.07 ± 0.79	1.53 ± 1.29	0.52 ± 0.66
Non-obese	2.55 ± 0.29	2.59 ± 0.24	2.67 ± 0.43	2.74 ± 0.59
T-test	**-5.478**	**-5.209**	**-2.391**	**-8.004**
P-value §	**< 0.001 ****	**< 0.001 ****	**0.026 ****	**< 0.001 ****

§ P-value has been calculated using independent t-test; ** Significant at $p < 0.05$ level.

Fig. 1. Distribution of Mean FGF2 measured over time comparing obese *vs* non-obese.

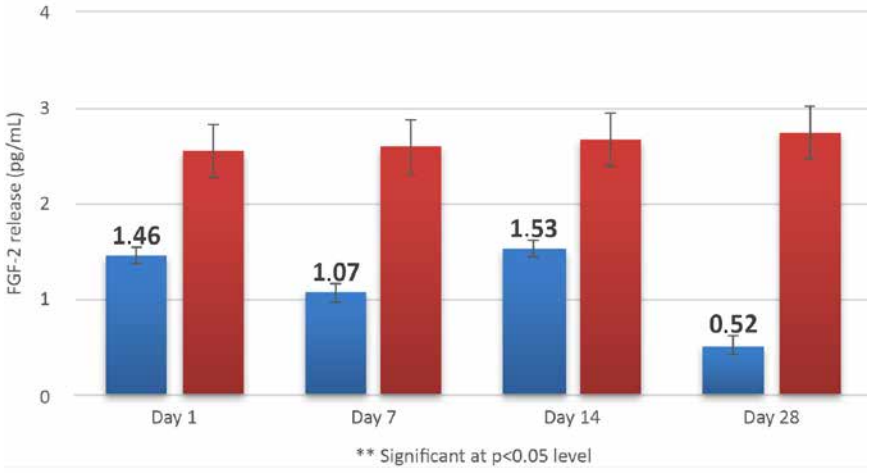
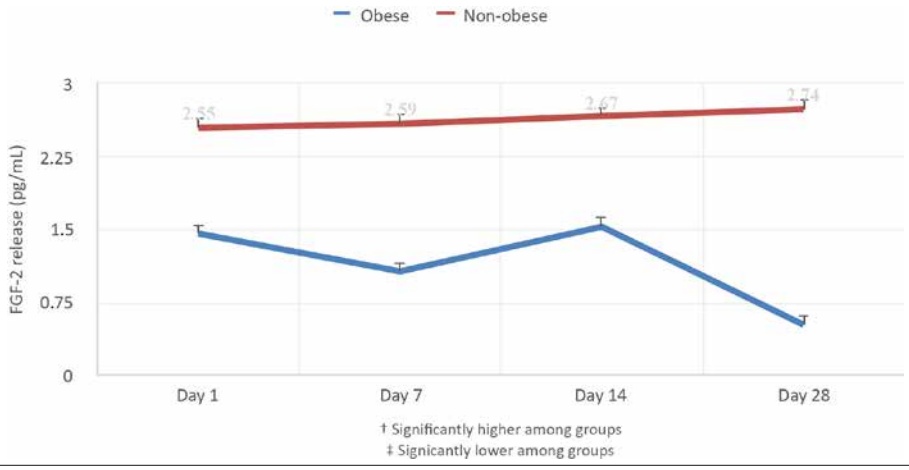


Fig. 2. FGF-2 trend line measured over time between obese and non-obese.



significantly lower on day 28 (mean 0.52) whereas day 14 was significantly higher (mean 1.53).

Table IIA described the Pearson correlation between FGF-2 concentration which was measured on different occasions such as; day 1, day 7, day 14 and day 28 among obese patients. It was determined that, no significant correlation was found among day1, day 7, day 17, and day 28 in relation to FGF-2 concentration.

In Table IIB where we also conducted Pearson correlation in regard to non-obese group. It was determined that the correlation between day 7 and day 1 was highly statistically significant ($r = 0.981$, $p < 0.001$).

Paired t-test was conducted at Table IIIA to assess the mean differences of FGF-2 which was measured over time among obese group. It can be seen that the paired t-test between day 1 and day 28 was statistically significant ($p = 0.001$). The difference was also statistically significant between day 7 and day 28 ($p = 0.048$) while the paired t-test between day 14 and day 28 was also statistically significant ($p = 0.004$).

For the normal group (Tab. IIIB), the paired t-test among FGF-2 measured over time were not statistically significant in different occasions.

Tab. IIA. Correlation (Pearson – R) between FGF-2 measured overtime among obese group (n = 15).

FGF-2	Day 1	Day 7	Day 14	Day 28
Day 1	1			
Day 7	0.282	1		
Day 14	-0.122	0.112	1	
Day 28	0.030	0.101	0.455	1

Tab. IIB. Correlation (Pearson – R) between FGF-2 measured overtime among non-obese group (n = 8).

FGF-2	Day 1	Day 7	Day 14	Day 28
Day 1	1			
Day 7	**0.981 ****	1		
Day 14	-0.251	-0.301	1	
Day 28	-0.302	0.589	0.632	1

** Significant at $p < 0.01$ level.

Discussion

The periodontal regeneration has become the common and most frequently used surgical periodontal therapy in periodontics. What has been proved positive technique or material for regeneration of lost periodontal structure is either improved in their concept or may not be used as frequently as before. Though there are many changes and advances in the adapted regenerative methods, the understanding of the concept of periodontal wound healing, cells required for the regeneration and other factors behind this therapeutic model are constantly

Tab. IIIA. Paired t-test between FGF-2 measured overtime among obese group (n = 15).

FGF-2	Mean differences	Mean standard error	95% CI of the difference	P-value
Pair 1				
Day 1 *vs* day 7	0.387	0.211	-0.066-0.839	0.088
Pair 2				
Day 1 *vs* day 14	-0.074	0.374	-0.876-0.729	0.847
Pair 3				
Day 1 *vs* day 28	0.935	0.212	0.480-1.391	**0.001 ****
Pair 4				
Day 7 *vs* day 14	-0.461	0.372	-1.258-0.337	0.236
Pair 5				
Day 7 *vs* day 28	0.549	0.253	0.007-1.091	**0.048 ****
Pair 6				
Day 14 *vs* day 28	1.009	2.976	3.709-1.647	**0.004 ****

** Significant at $p < 0.05$ level.

Tab. IIIB. Paired t-test between FGF-2 measured overtime among non-obese group (n = 8).

FGF-2	Mean differences	Mean standard error	95% CI of the difference	P-value
Pair 1				
Day 1 *vs* day 7	-0.038	0.027	-0.102-0.028	0.216
Pair 2				
Day 1 *vs* day 14	-0.117	0.207	-0.606-0.371	0.588
Pair 3				
Day 1 *vs* day 28	-0.192	0.259	-0.806-0.421	0.483
Pair 4				
Day 7 *vs* day 14	-0.079	0.196	-0.543-0.384	0.696
Pair 5				
Day 7 *vs* day 28	-0.155	0.241	-0.726-0.416	0.541
Pair 6				
Day 14 *vs* day 28	-0.075	0.162	-0.459-0.309	0.657

being updated and utilized for the clinical periodontal regenerative aspects [11].

Platelet-rich fibrin (PRF) first described by Choukroun et al. [12] is a new second generation of platelet concentrate. PRF provides a scaffold for cell migration and growth factors for promoting wound healing, bone regeneration, graft stabilization, wound sealing and hemostasis. Because the fibrin matrix is better organized, it is able to more efficiently direct stem cell migration and the healing program [13].

The concept of "natural bone regeneration" was proposed by Simonpieri et al. [14]. which includes regeneration of gingival tissue and bone volume through PRF membrane. Yuchao et al. [15]. showed that the use of PRF as the sole grafting material seems to be an effective modality of regenerative treatment for periodontal bonedefects.

In the present study we have taken into consideration that, obesity may have a role to play on the PRF. As of our knowledge and review of literature till today, it is assumed that, this is the first study to be conducted to evaluate the relation between the obesity and Fibroblast growth factor (FGF) in PRF of obese patients. In consideration of the effect of obesity on inflammatory cascade and cells, this type of study is well justified [16-18].

The traditional BMI classification underestimates risk in Asian and South Asian people. A separate guideline for this population classifies overweight as a BMI between 23 and 24.9 kg/ m2 and obesity as a BMI ≥25 kg/m^2 [19]. In the present study we have taken into consideration universally adapted definition for the obese and overweight patients If the BMI is 25.0 to < 30, it falls within the overweight range and If the BMI is 30.0 or higher, it falls within the obese range. Adapting the universally acceptable guideline for the obese it helps to compare the previous and future studies on same platform. Patient for the present study were recruited randomly from the outpatient department. Random selection of the patient helps in avoiding the sample bias which is helpful in the better interpretation of the results [20].

The sample size for the present study estimated as a total of 23 patients with 15 patients in the test group (obese) and 8 patients (healthy) group. Since it is the kind of first study to be conducted, for the sample size estimation, other studies done with almost similar background was chosen and minimal sample size required interpreting the acceptable results was taken into consideration.

Age group chosen for the study was between 25 to 50 years of age. Range of the age was acceptably wide to include as much as possible aged individuals, with caution taken to avoid the impact of aging on the growth factors. Age range was suitable to interpret the results with both the control and rest group were in the same age range with equal inclusion of age range. Thus, the probable worsening effect of aging in one group or better effect of aging in the younger group was avoided [21].

It is to be noted that, the blood sample for the measurement of FGF-2 was done on four intervals across a month. The assessment of growth factor over this defined period and intervals helps to overcome the one-time changes seen in FGF-2 level. It also helps to assess the true value and to avoid the one-time impact / on that one day impact of cellular changes affected by obesity on PRF growth factor. There is possibility of changing the inflammatory cascade, cytokines level and growth factor level depending upon the metabolic changes induced in the obesity. This four-time assessment will overcome all these barriers [16, 18, 22].

In the obese group of patients in the present study there was lower value of FGF-2 was seen over a month. There was significantly low level of FGF-2 was observed at first week and comparatively higher level observed at the end of the study period. The low level of FGF-2 in obese patients can be explained on the basis of impact of obesity on the other inflammatory cells. It is to be remembered that, there is always a viscous cycle between the inflammatory cell products like cytokine and growth factor which balances the formation and resorption of the periodontal tissue. When this balance is tilted towards inflammatory side, it predominates the destruction over the formation. Viceversa is seen when the growth factor dominates the cycle with formation of tissue is common. Present study results with low FGF-2 level in obese patient is justifiable , because its well-known that , in obesity adipocytes secret pro-inflammatory cytokines such as TNF-α and IL-6 [12] which stimulates the hepatic production of acute phase proteins such as C-reactive protein (CRP) and cause alteration in hosts immune response. Further it is also shown that, serum adiponectin which exert the anti-inflammatory effect are reduced and the resisting which exerts inflammatory effect are increased [22]. Over and above with all these, excessive ROS level and a decrease in antioxidant substances also has been reported. All this negative alteration in the immune response will shift the balance towards destruction and ability of cells like platelets to produce lesser growth factors. Thus, one of the possible reasons hypothesized for the lower level of FGF-2 seen in obese patient PRF is the shift in the inflammatory process towards negative balance [18].

Though the results can be taken into consideration to explain the relation between obese and normal patients PRF response, results can be improved in the future studies. Obese patient can be further classified according to BMI and comparison of the levels of growth factors helps us to determine the severity of obesity on level of growth factors. This further establishes and explains the role of obesity on FGF-2 level. Secondly, though the sample size chosen according to available previous almost similar observations studies, the sample size increased will help to establish the relation far better than this initial study. In the present study the gender demarcation was not done. Such gender differences if at all any seen if reported in terms of growth factor release will help to achieve better treatment strategy in obese male and obese female patient separately [23].

When obese patient PRF related growth factor compared to the non-obese or healthy patients it is observed that, there is study increase in FGF-2 in the stipulated study period. Absence of inflammatory triggers, positive cycle

of productivity is expected to release a better growth factor release in healthy non obese patients. Repair or regeneration overrides the destructive inflammatory process and balances the equation with the normal production of growth factor required for the normal turnover of a cell and tissue [24, 25].

Panahi et al. [26], conducted a cross-sectional study in patients with type 2 diabetes. Of the evaluated 141 subjects, 49 (34.8%) were categorized as having well-controlled diabetes, 66 (46.8%) had poorly controlled diabetes, and there were 26 subjects in the normal control group. Serum FGF21 concentrations were determined in all subjects using ELISA. Serum FGF21 level in the poorly controlled diabetic group was significantly higher than that in the well-controlled diabetic and the healthy control groups ($p = 0.02$) but there was no significant difference between the well-controlled and healthy groups. There was no significant association between serum FGF21 levels with lipid levels, presence of diabetic complications and BMI ($p > 0.05$).

In another study by Mashili et al. [27], levels of circulating FGF-21 in 207 overweight and obese Tanzanian males with or without type 2 diabetes mellitus (T2DM) were measured. They found higher levels of FGF-21 in people with T2DM compared to those without the disease. Based on statistical models, measures of adiposity explained up to 59% of the variability in FGF-21 levels in the circulation.

Conclusions

Within the limitation of the study the following conclusion can be drawn:

- FGF-2 measurement is lower in obese patients.
- It was registered a FGF-2 level increase in normal healthy or non-obese patients.
- When FGF-2 levels are compared between the intervals of one week, the FGF-2 level showed significant difference in obese patients.
- Study finding may be utilized in the treatment of periodontal regeneration in obese patients.
- The combination of PRF with regenerative therapy has been shown to be most promising for periodontal repair of boneand furcation defects, as well as soft tissue root coverage of gingival recession. However, the effect of PRF on pure bone regeneration remains questionable as many clinicians are unfamiliar with its use and thus requires more validating studies.

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Conflicts of interest statement

The authors declare no conflict of interest.

Authors' contributions

All authors contributed equally to this work.

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