ORIGINAL ARTICL

Low serum DEL-1 and high serum sP-sel levels in overweight and obese Subjects and their relation to platelet count

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ABSTRACT

Keyword: Developmental Endothelial Locus-1, Obesity, Platelet Count, Soluble P-selectin, Thrombosis.

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Background: Obesity is a major health issue with a thrombotic complications. Associated with increased soluble P-selectin (sP-sel) levels and decreased developmental endothelial locus-1(DEL-1) levels. **Objectives**: assessment of serum levels of DEL-1 in obese and overweight subjects and their relation to platelet count and sP-sel. **Methods:** 22 healthy controls (Group A), 22 overweight subjects (Group B), and 22 obese subjects (Group C) were enrolled in this case-control study. Serum levels of PLC, MPV, RBCs, HB, WBCs, Lymphocyte count, sP-sel, and DEL-1 were measured. **Results:** Serum levels of HB, DEL-1, and RBCs were lowest in group (C) and highest in group (A) with a statistically significant difference between these two groups. While, PLC,MPV, WBCs, lymphocyte count, and sP-sel serum levels were highest in group (C) and lowest in group (A). BMI, platelets, and WBCs count correlated positively with sP-sel and negatively with DEL-1 serum levels. sP-sel and DEL-1 showed a negative correlation with each other. **Conclusion:** Increased sP-sel levels and decreased DEL-1 levels in overweight and obese subjects might have a role in raising the risk of thrombosis and inflammation in these subjects.

INTRODUCTION:

Overweight and obesity are characterized by an excessive fat buildup that is harmful to one's health **(Lin and Li, 2021).**Over the past ten years, obesity rates have skyrocketed worldwide, to the point where some have dubbed it a pandemic **(Lim and Boster, 2023).** Numerous co-morbidities, including diabetes mellitus and cardiovascular illnesses, are linked to obesity **(Saalbach and Anderegg, 2019).**Anemia and obesity have recently been found to be strongly correlated **(Saad and Qutob, 2022).** According to **Purdy and Shatzel. (2021)** obesity and overweight are also associated with a higher risk of thrombosis and venous thrombo-embolism which is associated with elevated PLC.

Furthermore, those who are obese show an overall increase in platelet reactivity **(Puccini et al., 2023).**Increased inflammatory cytokines and other systemic changes seem to be the root cause of obesity's elevated platelet activation **(Goudswaard et al., 2022).**Fortunately, losing weight is an effective way to help obese people regain their physiological platelet function **(Barale and Russo, 2020).**It is now widely recognized that obesity increases the risk of thrombosis via activating platelets **(Barrachina et al., 2021).**

Shen et al. (2020) reported that there is an increase in the plasma levels of sP-sel after platelet activation, a protein derived from P- selectin on platelets' membrane. Accordingly, sP-sel levels are thought to reflect platelet activity **(Barale and Russo, 2020).**

Additionally, sP-sel has a crucial role in hemostasis and thrombosis by mediating platelet activation, producing pro-coagulant micro particles, promoting fibrin deposition, and subtly starting the coagulation cascade's extrinsic pathway **(Horváth et al., 2020).** Numerous medical conditions, such as coronary artery disease, myocardial infarction, stroke, hypertension, atrial fibrillation, and atherosclerosis, have been linked to high sP-sel levels **(Zhu et al., 2021).**Moreover, sP-sel may be a thrombosis biomarker **(Purdy et al., 2022).** According to **Horváth et al. (2020),** there is a positive association between sP-sel levels and body mass index (BMI). Increased sP-sel levels may be the cause of venous thrombo-embolism in obese patients**(Karsli et al., 2021).**Sincethey are markers of endotheliopathy and thrombosis predisposition **(Zhu et al., 2021).**

With no increase in bleeding, inhibition of sP-sel reduces thrombosis and vein wall fibrosis **(Purdy et al., 2022).**Therefore, it should now be considered a direct inducer of pro-coagulant activity linked to vascular and thrombotic disorders, rather than just a simple marker of platelet or endothelial activation **(Horváth et al., 2020).**

An endogenous anti-inflammatory glycoprotein called DEL-1**(Hajishengallis and Chavakis, 2019),**prevents neutrophil migration and recruitment and controls myelopoiesis by accelerating macrophage reprogramming and promoting inflammatory resolution **(Ziogas et al., 2020).**According to **Courtzelis et al. (2019),** DEL-1 thus controls both the onset and remission of inflammation. Patients with severe myocardial infarction and hypertension have lower DEL-1 levels **(Zhao et al., 2020).**

According to **Kim and Lee. (2021)** thrombosis and coagulation problems may emerge as a result of DEL-1 depletion. Because it can prevent thrombosis by inhibiting the development of platelet-monocyte aggregates and by acting as an inhibitor on platelet-derived microparticles, which are highly pro-coagulant molecules **(Yamanaka et al., 2019).** As well as inhibition of platelet monocyte aggregation**(Kourtzelis et al., 2019).**

When compared to healthy persons, the muscle of obese patients had lower DEL-1 levels also,in obese skeletal muscles, exercise was shown to raise DEL-1 mRNA expression levels in a time-dependent manner **(Kwon et al., 2020).**

To the best of our knowledge, until the time of our research, the levels of DEL-1 in the serum of obese and overweight patients have not been measured yet. So this study aimed to detect serum DEL-1 levels and to discover their relation to sP-sel and PLC in obese and overweight subjects.

SUBJECTS AND METHODS:

This study was done in collaboration between medical physiology and Internal Medicine departments at Aswan University. The Ethics Committee of the Faculty of Medicine at Aswan University granted approval for this study under Institutional Review Board (IRB) approval number 779423. The study was registered at clinical trials with registration number: NCT05864079

The participants were informed of the purpose, procedures, and risks associated with blood sample, including fainting during blood collection or fasting, and hematoma at the blood collection site. After that, each participant provided written informed consent. They have the option to leave the study at any moment without providing a reason. Participants' data were kept confident through coding of participants' data. All participants were informed of this study's final results.

Sample size was calculated using G*Power 3 software **(Faul et al., 2007),** with a power of 80% and type I error of 5% (α=0.05 and β=0.8) on two tailed test, the minimum required sample was 66 participants (divided into three equal groups, (**Group A**; Control with a BMI 18.5 to <25, **Group B**; overweight with a BMI from 25 to <30 and **Group C**; obese with a BMI of 30 or higher) to detect an effect size of 0.4 in the study primary outcomes.

Male persons aged from 18-65 were enrolled in this study. Healthy obese and overweight subjects were enrolled. Smokers, Diabetic, hypertensive persons, persons with heart failure, kidney, liver diseases, malignancies, and hyperthyroidism were excluded. Persons with a history of thrombo-embolic diseases and those who underwent major surgeries within 60 days are also excluded.

Blood samples were collected in plain tubes; serum was separated by centrifugation at 3000 rpm for 15 minutes. The clear non hemolyzed supernatant was separated and stored at -20 C until analysis.
Hemoglobin (HB), Red blood cells (RBCs), PLC, mean platelet volume (MPV), white blood cells (WBCs), and lymphocytic count in the serum were measured by Egytron, an automatic hematology analysis device.

Serum levels of sP-sel were measured by SELP kit (catalog No. ELK1274) purchased from ELK Biotechnology Co., Ltd., China by ELISA with intra-assay: coefficient of variability (CV)< 8% and inter-assay: CV≤ 10%

DEL-1 serum levels were measured by EDIL3 kit (catalog No. ELK7126) purchased from ELK Biotechnology Co., Ltd., China by ELISA with intra-assay: CV< 8% and inter-assay: CV≤10%

IBM Corp., situated in Armonk, NY, USA, provided SPSS version 23, which was used for the statistical analysis. Normality in the data was discovered by applying the Shapiro-Wilk test. Data that were normally distributed were expressed as mean ± standard deviation, One-way ANOVA and Pearson correlation tests were used to detect their significance difference. However, in the event that the distribution was not normal, the Kruskal-Wallis and Spearman correlation tests were used, and the median and interquartile range of the data were reported.

RESULTS:

BMI and serum levels of PLC, MPV, HB, RBCs, WBCs, and lymphocytes in the studied groups

There were statistically significant higher levels of BMI,PLC,HB,RBCs, WBCs, and lymphocytes in obese (group C) and overweight (group B)subjects when compared to controls (group A). Additionally, BMI, PLC, HB, and RBCs of group C subjects were statistically significantly higher than those of group B. Statistically higher levels of MPV were detected in group C when compared to group A**(table 1).**

No statistical significant difference in MPV levels was observed between group Band group A or between group B and group C.As well as, between group B and group C concerning WBCs or lymphocytes serum levels **(table 1).**

Table (1): BMI and Serum levels of PLC, MPV, HB, RBCs, WBCs, and lymphocytes in the studied groups

Data are expressed as mean ± standard deviation or median (interquartile range), **Group (A):** controls, **Group (B):** Overweight, **Group (C):** obese, **n:** number of persons, **BMI:** body mass index, **kg/m^2:** kilogram/meter^2,**RBCs:** red blood cells, **cells/mcL:** cells/micro liter, **MPV:** mean

	Group A (n=22)	**Group B (n=22)**	**Group C (n=22)**	**Significance**		
Age (years)	**36.2± 11.2**	**39.4±10**	**34.7±10.4**	**P1=0.570**	**P2 =0.885**	**P3 =0.304**
BMI (kg/m^2)	**20.7 (1.7)**	**26.5 (2.7)**	**33.1 (3.9)**	**P1<0.001***	**P2 < 0.001***	**P3 < 0.001***
PLC (×10^9 \ L)	**164.2± 14.5**	**251.4± 16**	**358.7± 27.5**	**P1<0.001***	**P2 < 0.001***	**P3 < 0.001***
MPV (fL)	**6.4± 2.5**	**8.1± 1.4**	**9.4± 3.1**	**P1 =0.064**	**P2=0.001***	**P3 = 0.216**
Hb (g/dL)	**13.8± 0.48**	**12.1±0.61**	**10.2± 0.72**	**P1<0.001***	**P2 < 0.001***	**P3 < 0.001***
RBCs (M/µL)	**5.66± 0.18**	**5.13± 0.32**	**3.85± 0.41**	**P1<0.001***	**P2 < 0.001***	**P3 < 0.001***
WBCs (×10^9 \ L)	**5± 0.34**	**6.2± 1.3**	**6.3± 1**	**P1<0.001***	**P2 < 0.001***	**P3 = 0.897**
Lymphocytes (×10^9 \ L)	**1.3± 0.26**	**2.3± 0.73**	**2.6± 0.86**	**P1<0.001***	**P2 < 0.001***	**P3 = 0.323**

platelet volume, **fl:** femtoliters, **PLC:** platelets count, **WBCs:** white blood cells,**10^9 \ L :**10^9 / liters, **P1:** probability value for Groups A vs group B, **P2:** probability value for difference between Groups A and C, **P3:** probability value for difference between Groups B and C. ***:** Statistically significant at $p \leq 0.05$, One-Way ANOVA test or Kruskal - Wallis was used.

sP-sel serum levels in the studied groups

Figure 1 describes levels of sP-sel in group A, group B, and group C subjects (193.6 ± 115.3pg/ml, 284.7 ± 72pg/ml, 564.8 ± 162.3pg/ml, respectively) that were statistically higher in group B when compared to group A as well as between group C and group A and between group B and group C.

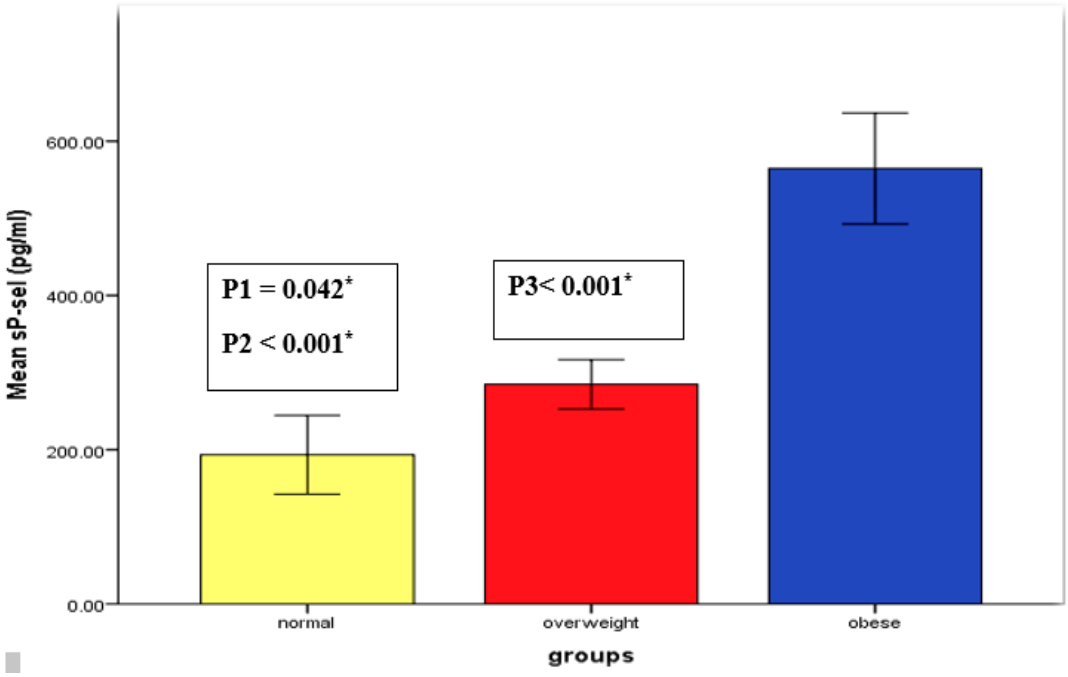


Figure (1): Serum concentration of sP-sel between studied groups

All data are expressed as Mean ± standard deviation, **sP-sel:** soluble p- selectin, **pg/ml:** pictogram/milliliter, **P1:** probability value for difference between normal and overweight, **P2:** probability value for difference between normal and obese, **P3:** probability value for difference between overweight and obese. ***:** Statistically significant at $p \leq 0.05$, One-Way ANOVA test was used.

Serum DEL-1 levels in obese, overweight, and controls

Statistically lower levels of DEL-1were reported in group C(1 ± 0.6ng/ml) when compared to group A (2.8 + 3 ng/ml) and to group B (2.1 + 1.2ng/ml), but there was no statistical significant difference of DEL-1levels between group A and group B **(figure 2).**

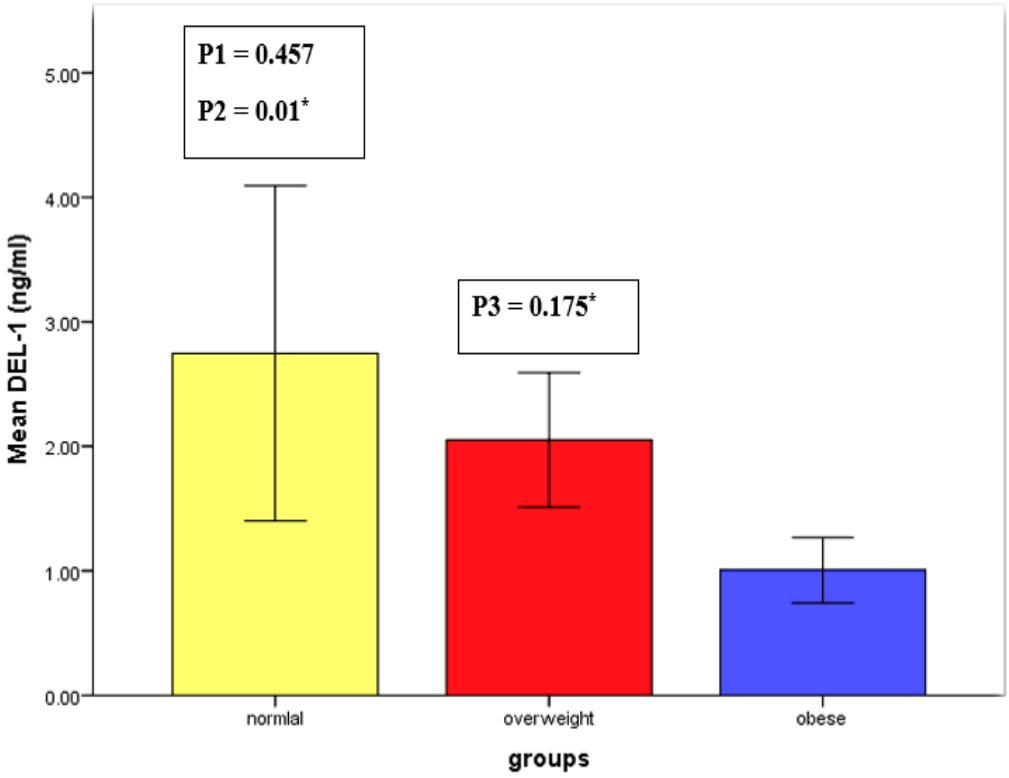


Figure (2): Serum concentration of DEL-1 between studied groups

All data are expressed as Mean ± standard deviation, **DEL-1:** developmental endothelial locus-1, **ng/ml:** nanogram/milliliter, **P1:** probability value for difference between normal and overweight, **P2:** probability value for difference between normal and obese, **P3:** probability value for difference between overweight and obese. ***:** Statistically significant at $p \leq 0.05$, One-Way ANOVA test was used.

Correlations between BMI, sP-sel and DEL-1 levels and serum concentration of PLC, MPV, HB, RBCs, WBCs, and Lymphocytes

Table 2 indicates a statistically significant inverse relationship between BMI and serum DEL-1, HB, and RBC levels. Additionally, statistically significant positive correlations were found between BMI and serum levels of MPV, WBCs, lymphocytes, PLC, and sP-sel.

There were statistically significant negative correlations between serum levels of sP-sel and serum levels of HB and RBCs, and statistically significant positive correlations were detected between serum levels of sP-sel and serum levels of MPV, PLC, WBCs, and lymphocytes **(table 2).**

Statistically significant positive correlations were reported between serum levels of DEL-1and serum levels of Hb and RBCs. However, a statistically significant negative correlation was reported between serum levels of DEL-1 and serum levels of PLC. But no statistically significant

correlations have been detected between serum levels of DEL-1 and serum levels of MPV, WBCs, or Lymphocytes**(table 2).**

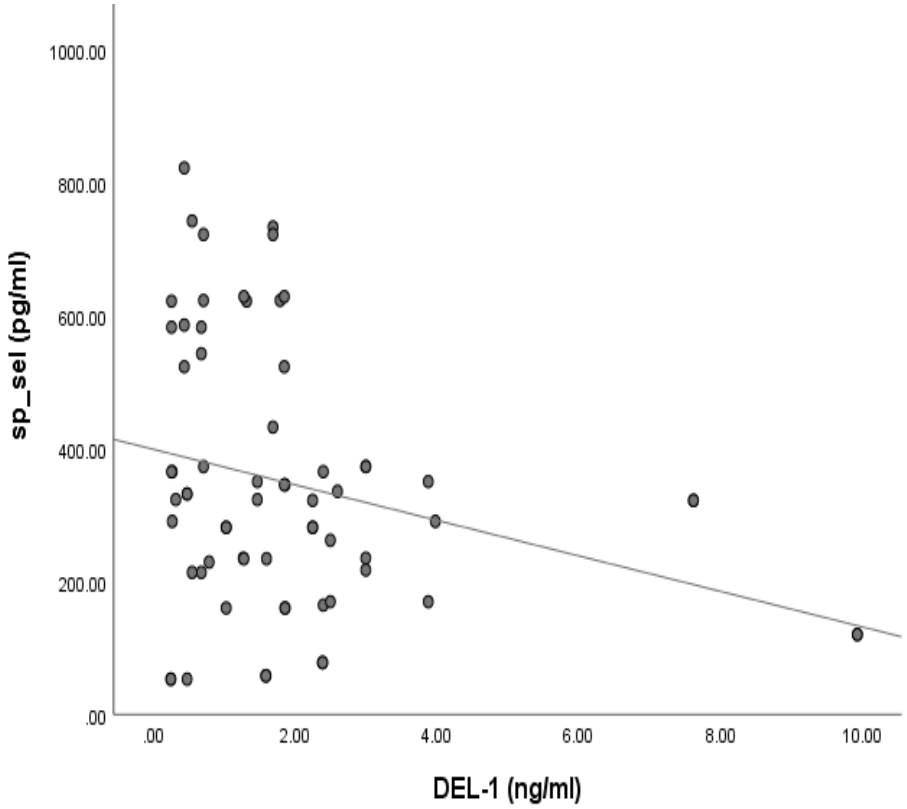
Table (2): Correlations between BMI, sP-sel and DEL-1 levels and serum concentration of PLC, MPV, HB, RBCs, WBCs, and Lymphocytes

	BMI (kg/m^2) (n=22)		**sP-sel (pg/ml) (n=22)**		**DEL-1 (ng/ml) (n=22)**	
	R	**P**	**R**	**P**	**R**	**P**
Platelets($\times10^9$ \ L)	**0.888***	**< 0.001***	**0.764***	**< 0.001***	**-0.305***	**=0.013***
MPV (fL)	**0.386***	**= 0.001***	**0.294***	**= 0.017***	**0.021**	**= 0.865**
Hb (g/dL)	**-0.895***	**< 0.001***	**-0.736***	**< 0.001***	**0.283***	**=0.021***
RBCs (M/µL)	**-0.869***	**< 0.001***	**-0.796***	**< 0.001***	**0.379***	**= 0.002***
WBCs ($\times10^9$ \ L)	**0.425***	**< 0.001***	**0.385***	**= 0.001***	**-0.020**	**= 0.875**
Lymphocytes ($\times10^9$ \ L)	**0.508***	**< 0.001***	**0.377***	**= 0.002***	**-0.192**	**= 0.123**

n: number of persons, **BMI:** body mass index, **kg/m^2:** kilogram/$meter^2$, **RBCs:** red blood cells, **cells/mcL:** cells/microliter, **MPV:** mean platelet volume, **fl:** femtoliters, **PLC:** platelets count, **WBCs:** white blood cells,**10^9 \ L :**10^9 / liters, **sP-sel:** soluble p- selectin, **pg/ml:** pictogram/milliliter, **DEL-1:** developmental endothelial locus-1, **ng/ml:** nanogram/milliliter, **R:** correlation coefficient, **P:**probability value.***:**Correlation is statistically significant at $P \leq 0.05$, Pearson correlation test was used.

Correlation between sP-sel and DEL-1 levels in the serum

A significant statistical negative correlation was detected between serum levels of sP-sel and serum levels of DEL-1 **(figure3**).



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DISCUSSION:

This study detected low serum DEL-1 levels in obese and overweight subjects that correlated with high sP-sel and PLC reflecting possible involvement of DEL-1 in increased thrombosis risk associated with obesity.

The results of this study indicated that, in comparison to the control group, the obese group and the overweight group had higher serum levels of WBCs and lymphocytes. These findings are consistent with earlier research by **Jeong et al. (2022)** and **Cohen et al. (2021),** which found that obese and overweight individuals had higher serum levels of WBCs and lymphocytes.

Serum WBC and lymphocyte levels were also found to positively correlate with BMI, and **Hsieh et al. (2023)** have indicated that a high BMI significantly influences an elevated WBC count. **Purdy and Shatzel. (2021)** found that there are several ways in which obesity-related leukocytosis happens, including the demargination of intravascular neutrophil, the acceleration of neutrophil release from bone marrow, and the stimulation of bone marrow granulopoiesis.

In comparison to the control group, the obese group and the overweight group had higher serum PLC and increased MPV. These findings are consistent with earlier research by **De Pergola et**

al. (2019) and **Ranucci et al. (2019),** which showed that subjects who are overweight or obese have higher PLC and MPV. Furthermore, **Jeong et al. (2022)** found a direct correlation between PLC and BMI.

According to **Ge et al. (2022),** PLC is elevated in inflammatory circumstances because it is an excellent indicator of systemic inflammation and the local immune response, and obesity is the underlying chronic inflammatory condition that causes this increase.

Furthermore, a study by **Warny et al. (2019)** found that obesity-related elevated PLC was linked to an increased risk of thrombosis.

In addition to a negative relationship between BMI and serum levels of HB and RBCs detected in this study, lower RBCs count and Hb levels were found in the obese group and the overweight group relative to the control group.

These findings are consistent with **Kohsari et al. (2021)** findings of low Hb levels and RBC counts in obese and overweight subjects, which they explained by pointing out that obesity is linked to an underlying anemic state caused by poor food quality and a lack of consumption of healthy ingredients. **Purdy and Shatzel (2021)** have noted that hypertensive obese individuals have greater Hb levels and a higher RBCs count. However, **Arshad et al. (2017)** could not find a correlation between BMI and either Hb level or RBCs count.

In comparison to the control group, the obese group and the overweight group had higher serum sP-sel levels. A positive correlation between BMI and sP-sel serum levels was also found in this study. This finding is consistent with the findings of **Bourassa et al. (2020),** who found that overweight and obese people have higher sP-sel levels. According to **Purdy et al. (2022),** obesity raises the level of sP-sel, which in turn causes platelet hyperactivity. Because sP-sel levels are thought to reflect platelet activity **(Barale and Russo, 2020).**

Serum levels of sP-sel were found to be positively correlated with MPV, PLC, WBCs, and lymphocytes. These findings concur with those of **Borgel et al. (2019),** who showed favorable associations between serum levels of MPV and PLC and sP-sel, suggesting that the latter is necessary for platelet aggregation and activation. **Comer et al. (2021)** also revealed that there was a positive correlation between serum levels of WBCs, lymphocytes and sP-sel, with higher levels of sP-sel observed under inflammatory conditions.

Nonetheless, this investigation found a negative relationship between the serum levels of sP-sel and the serum levels of HB and RBCs. This could be explained by the fact that sP-sel stimulates platelet-monocyte aggregation and activates platelets, which in turn indirectly increases inflammation **(Barale and Russo, 2020).**

Numerous inflammatory mediators are activated by these events **(Carestia et al., 2019).** These inflammatory mediators further contribute to the anemia of chronic disorders by inhibiting the development of erythroid cells, lowering serum HB levels, and reducing the number of RBCs **(Weiss et al., 2019).**

In this study, people who were overweight and obese had greater DEL-1 levels than the control group (group A). Also, a negative correlation has been observed between serum DEL-1 levels and BMI.

Skeletal muscles release a myokine called DEL-1 when they are working out, Accordingly, DEL-1 mRNA expression levels in human skeletal muscle are increased in response to exercise **(Kwon et al., 2020).**

The negative relationship between BMI and DEL-1 can be explained by taking into account that obesity is a complicated condition produced by a number of variables, primarily lower physical effort as in immobile everyday life and inefficient energy use.

To the best of our knowledge, this study is the first to measure the DEL-1 level in the blood of overweight and obese participants; however, **Kwon et al. (2020)** demonstrated that the muscle of obese patients had lower DEL-1 levels than those of healthy persons. Serum DEL-1 levels were found to be positively correlated with Hb and RBC levels. Since DEL-1 is an endogenous anti-inflammatory glycoprotein, this makes sense **(Kourtzelis et al., 2019).** Therefore, low DEL-1 levels are typically linked to underlying inflammatory states, and these inflammatory states lead to anemia, which is manifested as low levels of Hb and RBCs. DEL-1 and PLC serum levels, however, had a negative correlation with one another. Since thrombosis and coagulation problems can emerge as a result of Del-1 depletion and elevated PLC **(Kim & Lee, 2021).**

According to this study, there is a negative correlation between the tested groups' serum levels of DEL-1 and sP-sel. Due to the glycoprotein sP-sel being present on the surface of leukocytes and platelets. By changing neutrophil and monocyte activity, selectins accelerate and exacerbate thrombosis. They are important mediators of leukocyte and immune cell adhesion and transmigration into sites of inflammation **(Agrati et al., 2021).**

Given that DEL-1 also plays a significant role in immune regulation and the resolution of inflammation, it is possible that DEL-1 could be a useful target for treatment of a variety of inflammatory conditions **(Hajishengallis & Chavakis, 2019).** This negative connection can be explained by the conflict between the physiological roles of DEL-1 and sP-sel.

LIMITATIONS

There are several restrictions on this study. First, our results can be impacted by the fact that it is conducted at a single facility with a moderate sample size. Furthermore, while D-dimer is one of the markers used to assess the underlying thrombotic risk in various disorders, it is not measured in this study. Inflammatory markers, in addition, need to be detected. Furthermore, because activated platelets are important for thrombotic and inflammatory problems in obesity and overweight patients, measuring the quantity of activated platelets with flow cytometry may be helpful. Therefore, we believe that larger, multicenter investigations ought to be carried out in order to further corroborate the findings of our research.

CONCLUSION

Elevated concentrations of sP-sel and PLC, which are regarded as possible thrombosis risk factors, were seen in the serum of patients who were overweight and obese. It was discovered that the serum levels of DEL-1 in obese and overweight individuals were low, which generally controls inflammation and inflammatory markers, and that DEL-1 linked negatively with PLC and sP-sel. This could be a factor in thrombosis, inflammation-related problems, and the underlying chronic inflammatory state that is present in obese and overweight people.

ACKNOWLEDGEMENTS:

Authors thank all study participants as well as the Faculty of Medicine, Aswan University for its financial support to this research.

AUTHOR CONTRIBUTIONS:

All authors shared designing the study, manuscript typing, data analysis and revision.

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