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Research Article

Does obesity affect the plasma level of Plasminogen Activator Inhibitor-1? And does CO_2 pneumoperitoneum affect it?

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KEYWORDS

Obesity;
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Abstract *Background:* This prospective controlled study was designed to evaluate the effect of obesity on the plasma level of Plasminogen Activator Inhibitor-1 (PAI-1) and also to evaluate the effect of CO_2 pneumoperitoneum on the plasma level of PAI-1 in patients underwent laparoscopic surgery.
Methods: The study included two groups; first group (non obese) included 30 patients with normal average BMI underwent laparoscopic cholecystectomy while the second group included 30 obese patients with BMI > 30 kg/m^2 underwent laparoscopic band ligation or fundoplication surgery. Five ml of venous blood was collected from each patient in the non obese group once before induction of anesthesia while three venous blood samples (5 ml) were collected from each patient in the obese group as follows: first sample was taken before induction of anesthesia to compare it with the non obese group, second sample was taken after 1 h of CO_2 insufflations (to know the effect of CO_2 insufflations on PAI-1 level) and third sample was taken 1 week after surgery (to know the remaining effect in the postoperative period).
Results: The level of PAI-1 was significantly high (5.423 ± 2.5 ng/ml) in the obese patients compared to non obese patients (1.4 ± 0.641 ng/ml) (*P* value = 0.001). The level of PAI-1 was significantly high after

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CO_2 insufflations compared to baseline level (6.396 ± 2.542 ng/ml vs. 5.423 ± 2.5 ng/ml) in obese group (P value = 0.001). And this level also showed significant increase up to 1 week (6.01 ± 2.492 ng/ml vs. 5.423 ± 2.5 ng/ml) (P value = 0.028) in the obese group.

Conclusion: The PAI-1 level was higher in obese patients when compared to non obese patients. PAI-1 level was elevated after CO_2 insufflations and this elevation did not reach base line level up to 1 week after laparoscopic surgery.

1. Introduction

Obesity has been associated with several cardiovascular risk factors, such dyslipidemia, hypertension, glucose intolerance and premature atherosclerosis [1].

"PAI-1" level was significantly elevated in the plasma of obese individuals and correlates with BMI. These circulating levels of PAI-1 are elevated at an early stage of impaired glucose tolerance, resulting in type-2 diabetes and metabolic syndrome [2].

An association between an increase in PAI-1 and obesity has been described. And the decrease in BMI in morbid obesity shows a favorable effect on the fibrinolytic system due to a decrease in PAI-1 levels [3].

The connection between obesity and disordered haemostasis is well established. There is a strong link between inhibition of fibrinolysis in obese patients and the elevation of PAI-1 [4].

The regulation of fibrinolysis depends on the interaction of plasma fibrinolytic and anti-fibrinolytic proteins. Fibrinolysis depends on the enzymatic conversion of plasminogen to plasmin. This process is mediated by tissue-type and urokinase-type plasminogen activators. Plasma antifibrinolytic activity is primarily regulated by plasminogen-activator inhibitors (PAIs). PAI-1 is a single chain glycoprotein that contains from 379 to 381 amino acids. Endothelial and vascular smooth muscle cells are presumably the main sources of PAI-1 but other cells, such as platelets, hepatocytes, mesangial cells, fibroblasts, monocytes, macrophages, adipocytes, and stromal cells permeating the adipose tissue, have also been shown to secrete PAI-1 [5].

On the other hand, it is generally believed that laparoscopic surgery inflicts fewer traumas than open surgery. Many studies showed that the rise in peritoneal PAI-1 concentration during laparoscopy suggests an adverse effect of CO_2 insufflations [6].

The mesothelium cells exposed to flowing CO_2 released more PAI-1 than those exposed to pressurized CO_2 and this may be due to the combined effect of an increased expression of PAI-1 by CO_2 and a longer duration of active PAI-1 through acidosis suggests an adverse effect of the establishment and maintenance of pneumoperitoneum with CO_2 and these might provide a mechanism for peritoneal injury following laparoscopic surgery [7].

The aim of this study was to evaluate the effect of obesity on the level of PAI-1 and the effect of pneumoperitoneum due to CO_2 insufflations on the level of PAI-1.

2. Methods

This prospective controlled study was conducted after approval of the local ethics committee of El-Minia University Hospital, during the period from (May 2011) to (May 2012). A written informed consent was taken for every patient prior inclusion into the study.

The study included (60) patients. They were classified into two groups: first group (non obese) included (30) patients with normal average BMI underwent laparoscopic cholecystectomy. While the second group included (30) obese patients with BMI > 30 kg/m^2 according to the "WHO" classification system [8] underwent laparoscopic band ligation or fundoplication surgery. Five ml of blood was collected from each patient in the non obese group once before induction of anesthesia; Three venous blood samples were collected from the obese group as follows: first sample was taken before induction of anesthesia to compare it with the non-obese group, second sample was taken after 1 h of CO_2 insufflations and third sample was taken 1 week after surgery to measure the level of PAI-1.

We included, male and female patients, age range between 18 and 60 years old.

We excluded patients with severe medical diseases e.g. cardiovascular, pulmonary, hepatic and renal diseases.

After taking consent venous blood samples were collected to measure plasma level of PAI-1 as the following: first sample was taken before induction of anesthesia from the two groups (this sample was taken to compare between obese and non obese patient to show the effect of obesity on the plasma level of PAI-1 and it was considered the baseline value for each patient in the obese group), second sample was taken 1 h after CO_2 insufflations from the obese group (this sample was taken to know the effect of CO_2 insufflations on PAI-1 level) and the third sample was taken 1 week after surgery from the obese group (this sample was taken to know the remaining effect in the postoperative period).

Five ml of venous blood was collected in citrated tube then centrifuging the sample at speed 3000 rpm/min. The supernated was separated, assayed using kits supplied from Clinilab Company using enzyme immunosorbent technique with reference range from 0.031 to 2 ng/ml.

In the operating room standard monitors were connected before and after induction of anesthesia including ECG, pulse oximeter, capnography and non-invasive blood pressure. Intravenous line was inserted and the first sample was taken in the two groups. Induction of anesthesia was done by IV fentanyl (1.5–2 μg/kg IV), propofol (1.5–2 mg IV), rocuronium bromide (0.6 mg/kg) IV followed by intubation. Maintenance of anesthesia was achieved by sevoflurane 2–3% with 100% oxygen, and fentanyl infusion (1–2 μg/kg/h) allowing a range of decrease in the hemodynamic parameters within 20% of the baseline values. During surgery, a CO_2 insufflator (used for laparoscopic surgery) was connected to the patient. To investigate the effect of pressurized CO_2 on the PAI-1 level, a constant pressure of gas around (12–15 mm Hg) was

maintained throughout the procedure. After 1 h of CO_2 insufflations, the second sample was taken in the obese group. At the end of surgery, all anesthetic medications were stopped and the residual effect of muscle relaxant was reversed with neostigmine in a dose of (0.04 mg/kg) and atropine (0.4 mg per 1 mg neostigmine). After tracheal extubation, all patients were transferred to recovery room for monitoring of heart rate, blood pressure and oxygen saturation for 2 h then patients were transferred to the ward after complete recovery. The third sample was taken after 1 week.

2.1. Statistical analysis

Statistical analysis was conducted by using "SPSS" release 17 (Chicago, Illinois, USA). Descriptive statistics (mean, standard deviation "SD") were calculated. Comparative statistics between the two groups were applied. Unpaired *t*-test was used to compare the mean values between the two groups, while paired *t*-test was used to compare the mean values in the same group. Chi-square test was used to compare the difference of sex distribution between both groups. Significant result was considered when *P* value was less than (0.05).

3. Results

Total number of (60) patients were recruited for this study (30 patients in each group). There were no significant differences between the two groups as regard the age, sex distribution and the height. While; the body weight, BMI and duration of pneumoperitoneum showed significant differences between the two groups ($P = 0.001$) (Table 1).

The level of PAI-1 was significantly high (5.423 ± 2.5 ng/ml) in the obese patients compared to the normal average BMI patients (1.4 ± 0.641 ng/ml) ($P = 0.001$) (Table 2).

The level of PAI-1 was significantly high after CO_2 insufflations compared to baseline level (6.396 ± 2.542 ng/ml vs. 5.423 ± 2.5 ng/ml) in the obese group (*P* value = 0.001) and this level also showed significant increase up to 1 week after surgery compared to the baseline preoperative values (6.01 ± 2.492 ng/ml vs. 5.423 ± 2.5 ng/ml) (*P* value = 0.028) in the obese group (Table 3).

Table 2 Comparison of PAI-1 levels ng/ml between the two groups.

	Obese group ($n = 30$)	Non obese group ($n = 30$)	*P* value
Sample 1 (before anesthesia)	5.423 ± 2.5	1.4 ± 0.641	0.001

4. Discussion

In our study PAI-1 showed significantly high level in the obese patients when compared to the normal average body weight patients.

In agreement with our result McGill et al. has demonstrated that obese diabetic subjects show threefold elevated plasma concentrations of PAI-1 to healthy lean subjects [9].

Weight loss was associated with decrease in plasma PAI-1 which elevated again if weight was regained [10–13]. The same effect was achieved by surgical removal of fat [14].

Also our results showed that PAI-1 levels were significantly increased after CO_2 pneumoperitoneum. And this level showed significant increase up to 1 week after surgery compared to the baseline preoperative values.

In agreement with our result Matsuzaki et al. [15] who studied two groups of patients undergoing laparoscopic surgery group 1: low (8 mm Hg intraperitoneal pressure) and group II standard (12 mm Hg intraperitoneal pressure) and they found that PAI-1 in the 12 mm Hg group was significantly high after 1 h of CO_2 pneumoperitoneum than those in the 8 mm Hg group and it was significantly increased in both groups after 2 h of pneumoperitoneum.

Also in agreement with our result Bergström et al. [16] showed in their study that there was rise in peritoneal PAI-1 concentration during laparoscopy and they suggested that the elevation was an adverse effect of CO_2 insufflations which might affect peritoneal repair.

Bergström et al. [7] who exposed mesothelial cells to flowing CO_2 and pressurized CO_2 and they found that mesothelial cells exposed to flowing CO_2 released more PAI-1 than those exposed to pressurized CO_2 and they said that the combined effect of an increased expression of PAI-1 by CO_2 and a longer duration of active PAI-1 through acidosis suggests an adverse effect of the establishment and maintenance of pneumoperitoneum with CO_2 and these might provide a mechanism for peritoneal injury, adhesion development, and tumor dissemination following laparoscopic surgery and they recommended further research for the use of other insufflations gases.

In contrast to our study Brokelman et al. [16] how studied twelve patients undergoing laparoscopic gastric bypass surgery for morbid obesity and they take biopsies of the peritoneum at the start of procedure and each 45 min and they concluded that the level of PAI-1 was not affected throughout the procedure but the activity of tissue plasminogen activator decreased during the procedure reaching significant levels after 90 min of surgery.

Table 1 Patient's data in both groups.

	Obese group ($n = 30$)	Non obese group ($n = 30$)	*P* value
Age (y)	36.857 ± 7.087	34.791 ± 8.196	0.306
Sex (M/F)	11/19	10/20	0.897
Height (cm)	159.713 ± 4.959	162.350 ± 6.5845	0.085
Weight (kg)	111.427 ± 19.453	68.250 ± 10.547	0.001
BMI (kg/m^2)	42.997 ± 5.714	23.145 ± 2.145	0.001
Duration of pneumoperitoneum	79.29 ± 15.3	45.78 ± 20.92	0.001

Table 3 Comparison of PAI-1 levels ng/ml in the obese group.

	Obese group ($n = 30$)	P value
Sample 1 (before anesthesia)	5.423 ± 2.5	
Sample 2 (after pneumoperitoneum)	6.396 ± 2.542	0.001
Sample 3 (after 1 week)	6.01 ± 2.492	0.028

In conclusion, A PAI-1 level was elevated in obese patients compared to normal average patients. PAI-1 levels were elevated after CO_2 pneumoperitonium and this elevation did not reach the base line levels up to 1 week after surgery. However, further studies are needed to support these results and to evaluate the role of PAI-1 as a risk factor for the hypercoagulability state and how to eliminate this risk especially during the perioperative period and to do a correlation between the level of PAI-1 in relation to the duration of pneumoperitonium especially in prolonged laparoscopic surgery.

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