Migration Letters

Volume: 20, No: S12(2023), pp. 602-611

ISSN: 1741-8984 (Print) ISSN: 1741-8992 (Online)

www.migrationletters.com

The Effect of Diabetes Mellites Type 2 on the Cholelithiasis Patients

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Abstract

Back ground: Diabetes mellitus, is a syndrome that is characterized by hyperglycemia, it is one of the most common world's diseases, diabetes imposes different burdens due to the various complications associated with (Omoruyi et al., 2021).The current evidence has suggested that, the diabetes mellitus is associated with the gallstone's development, this could be attributable to the impaired of gallbladder emptying and a decreasing in secretion of bile salt from the gallbladder (C.-H. Chen et al., 2018). Aim: Study the effect of Diabetes on gallstones patients, as it is responsible for hyperglycemia, increasing triglycerides and gallstones diseases. Results: All biochemical markers, demonstrate highly significant difference ($p < 0.05$) compared to the control group as a total number and as males and females' groups separately, except for (I. R) in males' group. The same significant behavior was found when comparing both gender with each another, except for (BMI, HbA1C, ALP & bilirubin). The (ROC) curve for gallstones patients shows: All biomarkers show high significant statistical behavior and high % of area under the curve, with a good characteristic of validity for tests, except the validity characteristic for (BMI) for both genders, insulin for female and (I. R & GGT) for males. Spearman's nonparametric statistical correlation shows: Different positive and negative correlations coefficient for biomarkers, as the table showed. Conclusion: The results obtained concluded that overweight, insulin resistance, and high levels of leptin, which all indicate the metabolic syndrome, are the main contributors to the formation of gallstones. Abbreviations used: BMI: Body mass index, FBS: Fasting blood sugar, HbA1C: Hemoglobin A1 C, I. R: Insulin resistance, CRP: C-reactive protein, ALP: alkaline phosphatase, GGT: gamma-glutamyl Transferase, ROC: receiver operating characteristic, GD: gallstones disease and (MetS): Metabolic syndrome.

Keywords: *Cholelithiasis, Diabetes mellitus, metabolic syndrome & Biomarkers.*

1. Introduction

Diabetes mellitus is a chronic hyperglycaemia syndrome, it is the most common. Hyperglycaemia may have an effect on the ability of gallbladder contract to empty itself into the bile, and this will raise the risk for developing gallbladder diseases and stones (J. Wang et al., 2020).

Diabetes imposes different burdens due to the various complications associated with. The diabetes burdens imposed include, neuropathy, retinopathy, nephropathy, ischemic heart disease, peripheral vascular disease, and gallstones diseases. Estimates illustrate, that

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around (382 million) individuals suffered from Diabetes mellitus globally in (2013), the numbers expected to raise every year to reach (592 million) patients in (2035) (Guariguata L, et al., 2023). Investigators, identified different risk factors that could be associated with cholelithiasis' development of, such as increased (BMI), high triglycerides, reduced physical activity, hyperinsulinemia with even insulin resistance. All these factors may be associated with increased risk for cholelithiasis (Chandran et al., 2014).

The risk factors about developing gallstones should be concerned to reduce burdens on patients (Cui et al., 2012). There are different theories about the effect of diabetes and insulin resistance on gallbladder health. For example, people with diabetes tend to be obese or even overweight, in this case, the secretion of cholesterol in the bile increases, which in turn supports the accumulation of cholesterol and ultimately the formation of gallstones (Grundy, 2004).

There are increasing evidence, that suggest the metabolic syndrome which linked to hyperinsulinemia, insulin resistance with an elevated of triglycerides is associated with the increasing risk of gallstones diseases (Aune & Vatten, 2016). Another theory indicates that the formation of stones is due to autonomic neuropathy that caused by diabetes to the autonomic nerves. Where, the autonomic neuropathy controls the movement of the intestines and gallbladder. Thus, the bile stored will not release efficiently and the gallstones formed (Tahir, 2017). Moreover, gallstones disease and Metabolic syndrome (MetS) share most risk factors, the most common being abdominal obesity and insulin resistance, both of which are associated with increased cholesterol synthesis and biliary cholesterol hypersecretion. Therefore, it can be said with certainty that (GD) is a component of (MetS) (S. S. Kim et al., 2011). Many case-reports and cross-sectional studies reported considered that patients with gallstones disease are most likely to have metabolic syndrome than patients without (GD) (Di Ciaula et al., 2018). Moreover, the cholecystectomy may elevate the (MetS) risk. It was also found that, the prevalence of (GD) increased five folds in women had five (MetS), components compared to the women that are without MetS component.

Aim: Study the effect of Diabetes on gallstones patients through the biomarkers that indicate metabolic syndrome.

2. Research design and methods:

2.1 Research design

The study was performed on a representative sample of (127) participants at age (40-50) year, distributed as the following categories:

- (62) Diabetic's gallstones patients including (31 males & 31 females.
- (65) healthy control group including (32 male & 33 females).

Age and gender were matched for all participants.

2.2 Sample Collection

Venous blood samples were collected from each participant in standardized vacuum gel tube, under standardized conditions after fasting. Serum was obtained and then stored at -20ºC until the lab testing.

2.3 Methods:

Parameters were measured according to the following procedures:

1 - (TG, FBS, HbA1C, insulin, CRP, ALP & bilirubin) by Abbott chemiluminescence immunoassay, full automated using electroluminescence technology. The work steps were carried out according to the batch manufacturing procedures.

2- Leptin and gamma-glutamyl Transferase were measured using ELISA technique, (Sandwich-ELISA as a method). Using spectrophotometer at a wavelength of 450 nm.

3. Results and Discussion:

Metabolic syndrome, diabetes, dyslipidaemia, insulin resistance and hyperinsulinemia usually accompany cholelithiasis. It has been found that the prevalence of gallstone disease increases by (2-3) times in people with diabetes. Bile hyper saturation, high hepatic cholesterol secretion, and gallbladder dysfunction also lead to increased formation of gallstones (Sun, H. et al., 2022).

Statistical analysis was used to evaluate the change in the studied biomarkers, in order to demonstrate the effect of diabetes mellitus on the formation of gallstones.

3.1 Display the statistical analysis for gallstone patients compared to the control group as a total number.

All biochemical markers, demonstrate highly significant difference ($p < 0.05$) compared to the control group as a total number, as shown in the statistical analysis table (1). The results can be explained clinically as below:

Body mass index, Triglyceride and Leptin: The results showed that gallstone patients with diabetes were within the limits of onset of obesity according to the standard formula of the Quinlet Index (Nervi et al., 2006).

 between 30 and 39.9, it falls within obesity range.

To be overweight or being obesity may make individual to develop gallstones, especially in woman. Also, obesity people may have a large gallbladder, that might do not work well. Some studies shown that, people who have a lot of fat around the waist are likely to develop gallstones compared to those who have fat around the thighs and hips (Stokes & Lammert, 2021).

The main role of bile, is (digestion and absorption) of fat. Also, gallbladder plays an important physiological role fat, glucose and energy homeostasis, which may also affect the consumption of whole-body energy. It was found that, both cholecystectomy and gallstones disease can reduce the sensitivity of insulin (Acalovschi, G. E., et al., 2016) This confirm that, obesity is a common risk factor for both cholecystectomy and gallstones disease.

Gallstone have a high-risk for different diseases including colorectal cancer and biliary tract cancer. Most gallstones composed of cholesterol; thus, the cholesterol metabolism is important in the mechanism formation of gallstone. The increasing of (TG) level can be linked to the rapid nucleation for cholesterol crystals and cholesterol saturation (Wang, J., et al., 2020).

Leptin is derived from white adipose tissue located beneath skin, which suggest that, the adipose tissue is not only merely inert fat storage but, it is an endocrine gland. Leptin helps in maintain normal weight for a long-term basis, through the regulating of hunger and providing a (feeling full). The main function of leptin is represented by the balance between food intake and energy use (expenditure). So, the more serum level leptin an individual has, there will be more fat (Hontsariuk et al., 2020).

(FBS, HbA1C, insulin and insulin resistance: The results demonstrate highly significant increase in (FBS, HbA1C & I. R) and highly significant decrease in insulin for gallstones' patients with diabetes mellitus compared to the control group as a total number.

Gallstones disease and Metabolic syndrome (MetS) share most risk factors, the most common being abdominal obesity and insulin resistance, both of which are associated with increased cholesterol synthesis and biliary cholesterol hypersecretion. Therefore, it can be

said with certainty that GD is a component of (MetS) (Kim, S. S., et al., 2011). In cross-sectional study conducted (7570) subjects to associate between the development of gallstone and metabolic syndrome (MetS), it was found that, there are strongly association between gallstones disease and metabolic syndrome, and as the components of MetS increased (include, high Tg, obesity, I.R and high blood pressure), the prevalence of gallstone be higher (Pizza et al., 2020).

The excess weight found to be a major cause of metabolic syndrome. Where, the fat cells especially in the abdominal area increase free fatty acids, which in turn increase the levels of hormones and chemicals that affect the control blood sugar levels. As a result, the body may not respond well to insulin, and this is called insulin resistance. Also, free fatty acids increased triglyceride levels and blood pressure (Lonardo et al., 2015).

C-Reactive protein: The gallbladder inflammation may be triggered by, (1) obstruction of cystic duct by the gallstone's formation and the tissue damage subsequent, (2) release of lysolecithin from lipids membrane, (3) infection of ascending bacterial from the biliary fluid caused by the gallstone's obstruction, about (20%), of acute cholecystitis is caused by bacterial infection (Schuld & Glanemann, 2015a). This defect can cause a pathological congestion with tissue damage, and any natural host defense will be response to stimulate inflammation (Schuld & Glanemann, 2015b).

C-reactive protein levels found to be higher in bacterial infections compared to a virus, which can be helpful in directing antibiotic therapy. The higher (CRP) levels are reported with the more severity of tissue damage and more response stimulated inflammatory, it was reported that, a level of (CRP) more than (50–100 μg/ml), indicate a tissue damage (Antonelli & Kushner, 2017).

Alkaline Phosphatase, Gamma-glutamyl transferase and Bilirubin:

Gallbladder is very important in the hepatobiliary system, it works to help storing cholesterol acids manufactured in the liver and chemically modified bile salts, which work to dissolve fatty substances by acting as surfactants. Any disturbance in the activity or quantity of bile can lead to the accumulation of stones inside the gallbladder, which in turn may lead to congestion and tissue damage (Jones et al., 2017). When the stones originate within the bile duct, cholelithiasis is classified as primary, and becomes secondary when the stones leave the gallbladder, which is more common. There are many predictive factors for lithiasis including changes in test results such as, increasing (ALP), bilirubin and (GGT), (Costa et al., 2023). This finding is consistent with the pathophysiology of gallstones, where many factors contribute to cholestasis in the fourth decade of life (Chisholm et al., 2019).

The (GGT) is a cell surface enzyme. This enzyme is located in the human body in highest levels being in intestines, liver and gallbladder. Its level is elevated in liver/biliary tract disease, and it is one of the most important antioxidants. Increasing (GGT) level point to oxidative stress. Also, elevated levels of (ALP & GGT) is point to liver or the biliary tract disease. This is usually occurred by bile duct obstructions from conditions including gallstones and inflammation (Menekşe & Bas, 2023).

One study showed that (GGT) is directly linked (BMI), triglycerides, blood glucose levels and blood pressure, in addition to (LDL). The study, concluded that the risk of high (MetS) increases with high the level of (GGT). In addition (GGT) is a relatively inexpensive biochemical marker and is routinely evaluated as a component of liver function tests (Naidu et al., 2023).

3.2 Display the statistical analysis of biochemical markers according to the gender in gallstones patients.

The statistical study highlights on the relationship between gallstones disease and gender. All biochemical markers show highly statistically significant difference between males and females' groups, except (BMI, HbA1C, ALP & bilirubin).

Female gender is one of the most important risk factors. The rates of incidence are between two to three times higher in the women than in men. Where hormones such as progesterone and estrogen play important role in disease risk, progesterone inhibits the contraction of gallbladder, while estrogen causes supersaturation of cholesterol through the increasing of cholesterol secretion (Yang JL, et al., 2020).

Female gender, pregnancy, race, and age over (40) year are considered non-modifiable factors in the formation of gallstones, due to increased estrogen in addition to taking birth control pills, which tend to raise cholesterol levels in the bile. The female predominance is clear at a young age, however, the difference in gender become narrows with aging particularly, after the menopause (Kim, S. S., et al., 2011).

The fat distribution differs significantly between females and males. Where Women store white adipose tissue under the skin and thigh, while men store most of their adipose tissue in the visceral area or abdomen, which is a strong risk indicator for disease (Molina Morales et al., 2023).

Obesity is a global epidemic, now affecting more than a billion people. Adipose tissue differs in its distribution and function between women and men. Men are more susceptible to visceral obesity than women, and women, in contrast, have a higher percentage of fat. Where adipose tissue produces triglycerides (TG) in addition to secreting various hormones and contributing to the process of metabolic balance, (Palmer & Clegg, 2015).

3.3 Display Receiver-operating characteristic (ROC) curve analysis of gallstones patients, for both gender as a total number.

The future operating characteristic (ROC) curve, for gallstone patients with diabetes mellitus illustrate the assessment for the ability of biomarkers under the study to indicate the severity of the disease and their diagnostic suitability in case of diabetes mellitus. Where diabetes refers to a close association of the metabolic syndrome, which represents the main cause of gallstones. The effects can be documented by discussing table (3).

This curve shows that: All biomarker, show high significant statistical behavior and high percentage of area under the curve, also these markers show good characteristic of validity for all test in both genders, except:

- In Females' group: (Specificity% & NPV in (BMI), (Specificity%, PPV & NPV) in insulin.
- In Males' group: (Specificity%, PPV & NPV) in body mass index, (Specificity% & PPV) in insulin resistance and (NPV) in (GGT).

3.4 Display Spearman's Statistical Correlations for Biomarkers with Each other in gallstones patients.

Correlation is defined as a bivariate analysis, measures the association strength between two variables with the direction of the relationship. The value of the correlation coefficient is ranged between (+1 & -1). The value of (± 1) indicates a full degree of association between two variables. When the correlation coefficient value approaches zero, then the relationship between the variables will be weaker. The relationship direction between the variables is indicated by the sign of the coefficient; thus, positive sign indicates a positive relationship and negative sign indicates an opposite or negative relationship (Algina & Keselman, 1999).

The results in table (4), showed that some biochemical markers in gallstone patients show highly significant differences with positive or negative correlations that are (low, moderate or high). The different cells colors indicate different correlation strength as shown below:

TG correlations: Low positive with (leptin, insulin & I. R) and low negative with (GGT).

Leptin correlations: Low positive with (HbA1C), moderate positive with (FBS) and high positive with (I. R, CRP & ALP).

FBS correlations: Low positive with (CRP), moderate positive with (HbA1C & insulin), moderate negative with (GGT) and good positive with (I. R).

HbA1C correlation: Low negative correlation with bilirubin.

Insulin correlations: Excellent positive with (I. R), high positive with (CRP) and high negative with (GGT).

Insulin resistance correlations: High positive with (CRP) and high negative with (GGT).

C-reactive protein correlation: Highly negative with (GGT).

Alkaline phosphates correlation: Highly positive with (GGT).

GGT correlation: Low negative with bilirubin.

The correlation between biochemical markers, confirm the association of diabetics and gallstones formation as many previous studies indicated for.

The gallstone disease considered as a chronic disease which consumes a lot of medical resources and economic. It affects the patients' life quality and associated with new potential risks, such as pancreatitis, biliary tract obstruction, development of cholecystitis and may finally cause gall bladder cancer. Studies suggest firstly diabetes mellitus (DM) as closely related reason for gallstones incidence, in other word all diagnostic factors of metabolic syndrome (Lin et al., 2014).

Insulin Resistance, founds to poor gallbladder function, and affects the cholesterol amount, therefore any weakness in the functioning of the gallbladder puts the metabolism at great risk, in addition to the fact that bile is required to safely remove heavy metal toxins. Moreover, the epidemiological studies reported the high HbA1c is associated significantly with the oxidative stress (Moradi et al., 2012).

Table (1): Statistical analysis of biomarkers for gallstone patients compared to the control group as a total number.

Biomarkers	Study Groups as a total number		*P-value**
	Control = 65 mean ± SD	gallstone patients with diabetes mellitus = 62 mean ± SD	Control Vs gallstone patients with diabetes mellitus
BMI	24.3 ± 2.95	30.16 ± 4.2	0.0001
TG	127.738± 10.744	220.727 ± 11.898	0.0001
Leptin	5.767 ± 2.313	22.57 ± 5.531	0.0001
FBS	89.277 ± 8.469	189.758 ± 12.605	0.0001
HbA1C	4.643 ± 0.577	8.733 ± 1.180	0.0001
Insulin	14.298 ± 4.201	8.488 ± 2.056	0.0001
I. R	3.156 ± 0.998	4.000 ± 1.086	0.0001
CRP	5.652 ± 0.633	63.052 ± 12.359	0.0001
ALP	70.323 ± 8.154	202.26 ± 11.88	0.0001
GGT	27.053 ± 5.553	59.318 ± 12.600	0.0001
Bilirubin	0.671 ± 0.162	1.93 ± 0.48	0.0001

*Using One – Way Anova; $P < 0.05$ considered to be statistically significant.

Table (2): Statistical analysis of biomarkers for gallstones patients with diabetes mellitus, as (male and female) number compared to the control group

Bio-Markers	Groups				*P- value*		
	Control		Gallstones patients		Control male Vs Patients male	Control female Vs Patients female	Male patients Vs female patients
	Male = Mean± SD	Female = Mean± SD	Male = Mean± SD	Female = Mean± SD			
BMI	23.494 ± 2.91	25.401 ± 2.63	30.37 ± 7.269	29.9 ± 2.811	0.005	0.0010	0.388
TG	127 ± 9.72	141 ± 6.13	217 ± 11.2	224 ± 11.5	0.0001	0.0001	0.018
Leptin	3.86 ± 0.341	8.52 ± 0.627	17.487 ± 1.10	27.647 ± 2.13	0.0001	0.0001	0.016
FBS	90.5 ± 8.73	88.5 ± 8.35	195 ± 13.7	194 ± 9.36	0.0001	0.0001	0.003
HbA1C	4.45 ± 0.546	4.95 ± 0.489	8.80 ± 1.21	8.66 ± 1.15	0.0001	0.0001	0.635
Insulin	14.0 ± 4.27	14.0 ± 1.26	6.73±0.603	10.2 ± 1.36	0.0001	0.0001	0.0001
I. R	3.13 ± 1.04	3.08 ± 0.473	3.09±0.417	4.92 ± 0.707	0.818	0.0001	0.0001
CRP	5.98 ± 0.620	5.67 ± 0.510	53.5 ± 8.37	72.6 ± 7.03	0.0001	0.0001	0.0001
ALP	78.8 ± 5.50	67.8 ± 4.59	198.345 ± 1 8.7	206.185 ± 15.4	0.0001	0.0001	0.382
GGT	33.5 ± 2.55	23.4 ± 1.44	71.1 ± 4.48	47.6 ± 4.17	0.0001	0.0001	0.0001
Bilirubin	0.791 ± 0.133	0.691 ± 0.135	1.84 ± 0.684	2.028 ± 0.645	0.0001	0.0001	0.793

P- is calculated by using the Mann-Whitney test.

Table (3): Receiver-operating characteristic (ROC) curve analysis of biomarkers for gallstones patients without (DM) as a total number.

Gallstones' Patients												
Male							Female					
NPV	PPV	Specificity %	Sensitivity %	*P*-value AUC = 0.05	Area under the curve	Bio-markers	Area under the curve	*P*-value AUC = 0.05	Sensitivity %	Specificity %	PPV	NPV
26	42	59	75	0.0001	0.737	BMI	0.654	0.011	99	17	84	2
78	99	99	75	0.0001	0.999	TG	0.999	0.0001	81	99	99	84
93	83	94	84	0.0001	0.999	Leptin	0.999	0.0001	85	99	99	87
95	67	85	98	0.0001	0.999	FBS	0.999	0.0001	97	85	87	97
98	90	92	99	0.0001	0.999	HbA1C	0.999	0.0001	99	91	92	99
82	92	93	79	0.0001	0.954	Insulin	0.773	0.0001	76	33	53	58
60	53	28	81	0.013	0.354	I. R	0.981	0.0001	81	96	95	83
83	99	99	80	0.0001	0.999	CRP	0.999	0.0001	79	99	99	83
77	90	94	81	0.0001	0.999	ALP	0.999	0.0001	82	99	99	85
59	67	88	73	0.0001	0.999	GGT	0.999	0.0001	82	99	99	85
80	96	97	75	0.0001	0.960	Bilirubin	0.994	0.0001	70	99	99	77

Table (4): Nonparametric Spearman's statistical correlation coefficient for biomarkers in gallstone patients with diabetes mellitus

marker/ variable		Leptin	FBS	HbA1C	Insulin	I.R	CRP	ALP	GGT	Bilirubin
TG	r	0.266	0.128	- 0.055	0.260	0.274	0.175	0.063	- 0.290	0.086
	P	0.031	0.304	0.659	0.035	0.026	0.160	0.613	0.018	0.490
Leptin	r		0.322	0.266	- 0.024	0.742	0.751	0.645	0.043	0.202
	P		0.008	0.031	0.847	0.0001	0.0001	0.0001	0.731	0.103
FBS	r			0.402	0.350	0.537	0.293	- 0.016	- 0.344	- 0.034
	P			0.001	0.004	0.0001	0.017	0.897	0.005	0.786
HbA1C	r				0.014	0.085	- 0.181	- 0.093	0.054	- 0.253
	P				0.909	0.496	0.147	0.458	0.667	0.041
Insulin	r					0.969	0.654	0.215	- 0.735	0.220
	P					0.0001	0.0001	0.084	0.0001	0.076
I.R	r						0.678	0.196	- 0.754	0.196
	P						0.0001	0.114	0.0001	0.115
CRP	r							0.182	- 0.669	0.165
	P							0.144	0.0001	0.185
ALP	r								0.678	0.196
	P								0.0001	0.114
GGT	r									- 0.244
	P									0.048

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