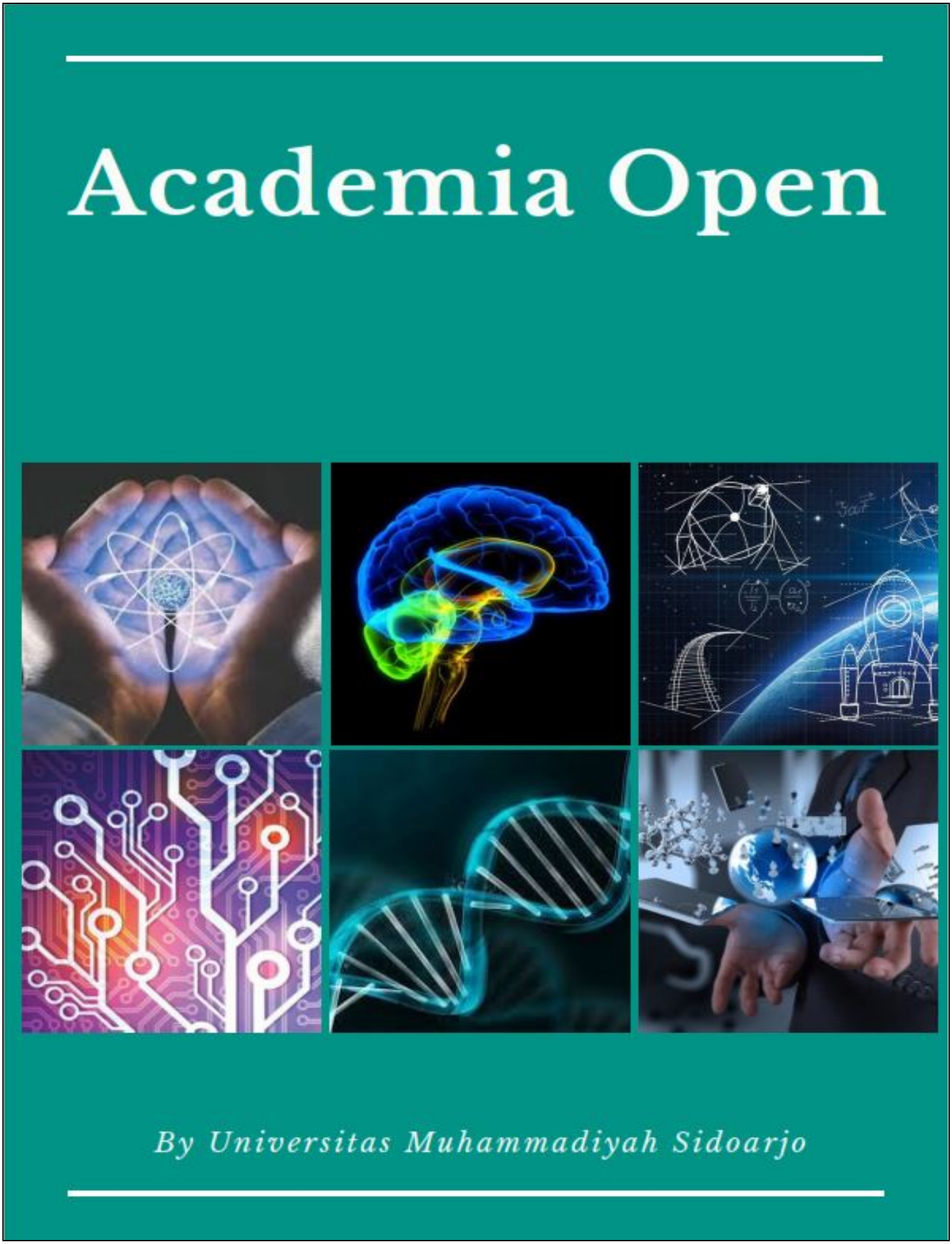
Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

Table Of Content

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)



ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

Originality Statement

The author[s] declare that this article is their own work and to the best of their knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the published of any other published materials, except where due acknowledgement is made in the article. Any contribution made to the research by others, with whom author[s] have work, is explicitly acknowledged in the article.

Conflict of Interest Statement

The author[s] declare that this article was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright Statement

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

EDITORIAL TEAM

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

Article information

Check this article update (crossmark)

Check this article impact (*)

Save this article to Mendeley

(*) Time for indexing process is various, depends on indexing database platform

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

Relationship Coagulation Indicator with Hyperglycemia and Hyperlipidemia in Diabetes Mellitus Disease

Hubungan Indikator Koagulasi dengan Hiperglikemia dan Hiperlipidemia pada Penyakit Diabetes Melitus

Wisam Abdan Wawi AL Abdullah, wisam.wawa@qu.edu.iq, (1)
, Iraq

(1) Corresponding author

Abstract

Metabolism dysfunction including hyperglycemia and hyperlipidemia in diabetes mellitus case are crucial factors in developing vascular diseases, platelet activation and hypercoagutable state. Increasing coagulation factors and hypercoagulability were reported in diabetes mellitus patients which due to increase of coagulation factors that resulted in prothrombotic state and extension of thrombolytic lysis in diabetes patients. Thus, this works amid to exam the association between coagulation index's with hyperglycemia and dyslipidemia in diabetes mellitus patients. FBG, HbA1c, PT, APTT, INR, D-dimer, platelets and MPV values were showed significant increase in diabetic's patients compared with their levels of healthy. Lipids profiles, AIP and TC/HDL ratio were found significantly higher in patients they were suffering from diabetic. Person correlation analysis presented a strong association between prothrombin time and (FBG, PLT, TC and LDL). MPV and AIP were a moderate positive correlate with prothrombin time. Prothrombin time was a weak correlated with HbA1c, TG, HDL and TC/HDL ratio. However, D-dimer and VLDL were negatively associated with prothrombin time. APTT value presented a strong positive association with FBG and LDL, a moderate positive relationship with AIP and TC/HLD. There was a weak positive association between APTT value HbA1c, D-dimer, PLT, MPV, TC and HDL. However, TG and VLDL were negatively correlated with APTT value.

Highlights:

1. Metabolic Dysfunction: Hyperglycemia and dyslipidemia increase coagulation factors in diabetes.
2. Key Findings: Significant rise in PT, APTT, D-dimer, lipid profiles, and MPV.
3. Correlations: Prothrombin time associates strongly with FBG, PLT, TC, and LDL.

Keywords: diabetes, Prothrombin time, activated partial thromboplastin, atherogenic index of plasma, coagulation factors

Published date: 2025-01-19 00:00:00

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

Introduction

Diabetes mellitus is a metabolic syndrome described through elevated blood sugar levels (hyperglycemia), resulting from decreased insulin secretion or dysfunction of insulin receptor action [11], [20], [24]. Diabetes is correlated with vascular damage, metabolic disorders, and thrombotic complications [11], [19], [23]. Complications of diabetes can lead to several pathophysiological conditions, including cardiovascular diseases, nephropathy, neuropathy, retinopathy [18], inflammation, dyslipidemia [25], [35], thrombophilia, oxidative stress, endothelial dysfunction, atherogenic, and procoagulant states [11], [55], [67]. Metabolic dysfunction, including hyperglycemia and hyperlipidemia in diabetes mellitus, are crucial factors in developing atherosclerosis, vascular diseases, platelet activation, and hypercoagulable states [11], [14], [58], [71]. Increased coagulation factors and hypercoagulability have been reported in diabetes mellitus patients [11], [44], resulting from elevated coagulation factors like factor VII, proinflammatory cytokines, and fibrinogen, which contribute to a prothrombotic state [11], [16], [23]. Hyperglycemia leads to glycation of hemoglobin, fibrinogen, clotting proteins, and prothrombin, causing dysfunction in the coagulation pathway [11], [60], [75]. Insulin resistance, lipotoxicity, and high glucose levels in diabetes mellitus primarily affect vessel walls, leading to increased inflammation, enhanced platelet aggregation, endothelial dysfunction, and altered coagulation factors [13], [76]. These changes contribute to microvascular complications, which increase the risk of thrombosis and vascular diseases in diabetes [5], [54].

Diabetic patients suffer from lipid disorders, which increase the risk of atherosclerosis and heart problems [36], [37], [70]. Studies have assumed a hypercoagulable state is associated with hypercholesterolemia [77]. Poredos and Jezovnik reported that endothelial damage and prothrombotic states are correlated with blood lipids, which impact coagulation factors, platelet activity, and vascular endothelium, further modulating the function and expression of thrombolytic and fibrinolytic factors [62]. Studies found that increasing blood lipid concentrations is associated with upregulation of coagulation factors [38]. Furthermore, patients suffering from insulin resistance have high visceral lipids [73], which have been shown to be related to increased activity of FVIII, FIX, and FVII [31]. Different studies have observed coagulation abnormalities related to hyperglycemia and dyslipidemia. Therefore, the current work aimed to examine the association between coagulation indexes with hyperglycemia and dyslipidemia in diabetes mellitus patients.

Methods

Study design: 60 blood specimens were taken from diabetes mellitus patients aged 40-65 year. Another 56 samples were collected from healthy people (non-diabetes), they used as a control group aged 40-65 year. These samples were collected from people who frequent the health center specialized in regulating and treating diabetes at Al-Diwaniyah Teaching Hospital/ Iraq. Current work was done during a period from 15 November 2022 to 20 May 2023. Blood was drawn from a vein after overnight fasting, and placed in special test tubes. Each sample was divided into three tubes; the first tube was free of anticoagulant to obtain blood serum. To conduct a blood sugar test, as well as to measure fat concentration. The second tube contained the anticoagulant sodium citrate at a concentration in order to conduct some blood clotting analysis coagulation markers. The third tube also contained the anticoagulant, which is EDTA, to conduct platelets analysis.

Laboratory analysis: Blood glucose analysis was detected through an available kit (Spinreact, Spain). An available kit was used to measure HbA1c level using by Roche Diagnostics Cobas analyzer. Lipids profile; cholesterol (TC), triglycerides (TG), lipoproteins including (HDL-C, LDL-C) estimated using enzymatic colorimetric technique by special reagents with Roche Modular P800 Chemistry Analyzer. VLDL-C was determined by (triglyceride/5). The formula log (TG/HDL-C) ratio was used to calculate atherogenic index of plasma (AIP). TC/HDL ratio was calculated by divided TC value on HDL value. Coagulation indicates (PT), APTT and D-dimer were estimated by standard kits and measurement using automated analyzer ACL TOP 700. International normalized ratio (INR) was estimated by the following formula: PT (patient)/PT (healthy). Hematology parameters (platelet PLT and mean platelet volume MPV) were achieved using automatic cell counter (Thermo Fisher Scientific).

Statistics analysis: Comparisons were drawn between patients and healthy groups using an unpaired t-test by Graph Pad Prism (USA). The data were described statistically (Mean± Standard error). Correlation coefficient test was calculated between coagulation parameters and physiological indicators in diabetes patients group.

Result and Discussion

Result

The diabetes patients showed significantly increasing ($p \leq 0.05$) in fasting blood glucose level (227.4±27.11) comparison with control subject (105.8±5.20). A significant greater HbA1c value was showed in patients (8.65±1.50, $p \leq 0.001$) compared to the healthy subject (5.32±1.17). Cholesterol level (TC) was increased significantly in diabetic patients (215.2±13.56, $p \leq 0.05$) in contrast to control samples (128.7±2.72). Triglyceride

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

concentration (TG) significantly increased in patients (160.3±20.17, p≤0.05) compared with healthy (106.1±9.85). While, HDL level was significantly decreased (23.55±0.27, p≤0.01) in patients compared with level of un-patients samples (27.68±1.69). Level of LDL significantly elevated in diabetic patients (126.0±6.12, p≤0.05) compared with healthy level (99.23±9.56). VLDL level was highly significant increase in patients (31.04±0.75, p≤0.01) comparing with level control (24.38±1.52). A significant differ was obtained (p≤0.05) between diabetic and healthy group in AIP value (0.78±0.05 and 0.59±0.04, respectively). TC/HDL ratio was significantly higher in patient group (9.37±0.67, p≤0.05) compared with control (5.10±0.63), Table (1).

parameters	Control	Diabetes	P value
FBS (mg/dl)	105.8±5.20	227.4±27.11	*0.0368
HbA1c %	5.32±1.17	8.65±1.50	***0.0002
TC (mg/dl)	128.7±2.72	215.2±13.56	*0.0360
TG (mg/dl)	106.1±9.85	160.3±20.17	*0.0412
HDL (mg/dl)	27.68±1.69	23.55±0.27	**0.0017
LDL (mg/dl)	99.23±9.56	126.0±6.12	*0.0286
VLDL (mg/dl)	24.38±1.52	31.04±0.75	**0.0003
AIP (mg/dl)	0.59±0.04	0.78±0.05	*0.0276
TC/HDL (mg/dl)	5.10±1.63	9.37±3.67	*0.0260

Table 1. *Comparison of physiological and lipid profiles between controls blood samples and diabetes patients (Mean± SD). Where ***p≤0.001, **p≤0.01, *p≤0.05.*

PT was significantly prolonged in diabetes mellitus patients (16.64±0.43, p≤0.05) when paralleled to group of the control (14.28±0.21). APTT value in patients was higher (37.03±3.17, p≤0.05) than those in control group (31.23±4.56). INR values were significantly differ (p≤0.05) between diabetic and non-diabetic groups (1.98±0.07 and 1.04±0.05, respectively), Table (2). D-dimer value significantly increased with diabetic patients (416.6±45.31, p≤0.001) compared with the healthy group (209.4±13.41). Platelets value presented higher level in patients group (265.9±14.14, p≤0.05) than non-patients group (220.9±13.17). MPV exhibited no significant differences (p≥0.05) between patients group (9.40±0.23) and control group (8.79±0.85), Table (2).

Parameters	Control	Diabetes	P value
PT (sec)	14.28±0.21	16.64±0.43	*0.0156
APTT (sec)	31.23± 4.56	37.03± 3.17	* 0.0270
INR (sec)	1.04±0.05	1.98±0.07	*0.0241
D-dimer	209.4±13.41	416.6±45.31	***0.0161
PLT (x103/ul)	220.9±13.17	265.9±14.14	*0.0411
MPV (fl)	8.79±0.85	9.40±0.23	ns0.4717

Table 2. *Comparison of coagulation markers between controls blood samples and diabetes patients (Mean± SD). Where ***p≤0.001, **p≤0.01, *p≤0.05, ns p≥0.05*

A strong positive association was detected between prothrombin time and FBG in patients of diabetes (r=0.6232, p-0.048). HbA1c had a weak positive relationship with prothrombin time in diabetics group (r = 0.2486, p-0.412). However, D-dimer was noted a weak negative association with prothrombin time (r = - 0.2256, p-0.530). A strong positive association was found between prothrombin time and PLT (r = 0.6338, p-0.015). MPV was observed a moderate positive related with PT (r = 0.5061, p-0.033) in patients of diabetes, Table (1) and Figure (1A). APTT value presented a strong positive association with FBG (r = 0.6233, p-0.039). APTT was a weak positive association with HbA1c (r = 0.1404, p-0.324), D-dimer (r = 0.2896, p-0.036), PLT (r = 0.2518, p-0.055) and MPV (r = 0.2102, p-0.049) in diabetic patients, Table (3) and Figure (1B).

Parameters	PT (Sec)	P-value	APTT (Sec)
FBG (mg/dl)	0.6232	*0.048	0.6233
HbA1c %	0.2486	ns0.412	0.1404
D-dimer	-0.2256	ns0.530	0.2896
PLT (x103/ul)	0.6338	*0.015	0.2518
MPV (fl)	0.5061	*0.033	0.2102

Table 3. *Pearson's correlation was analyzed between coagulation markers and physiological parameters of diabetes patients. Where *p≤0.05, ns p≥0.05*

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

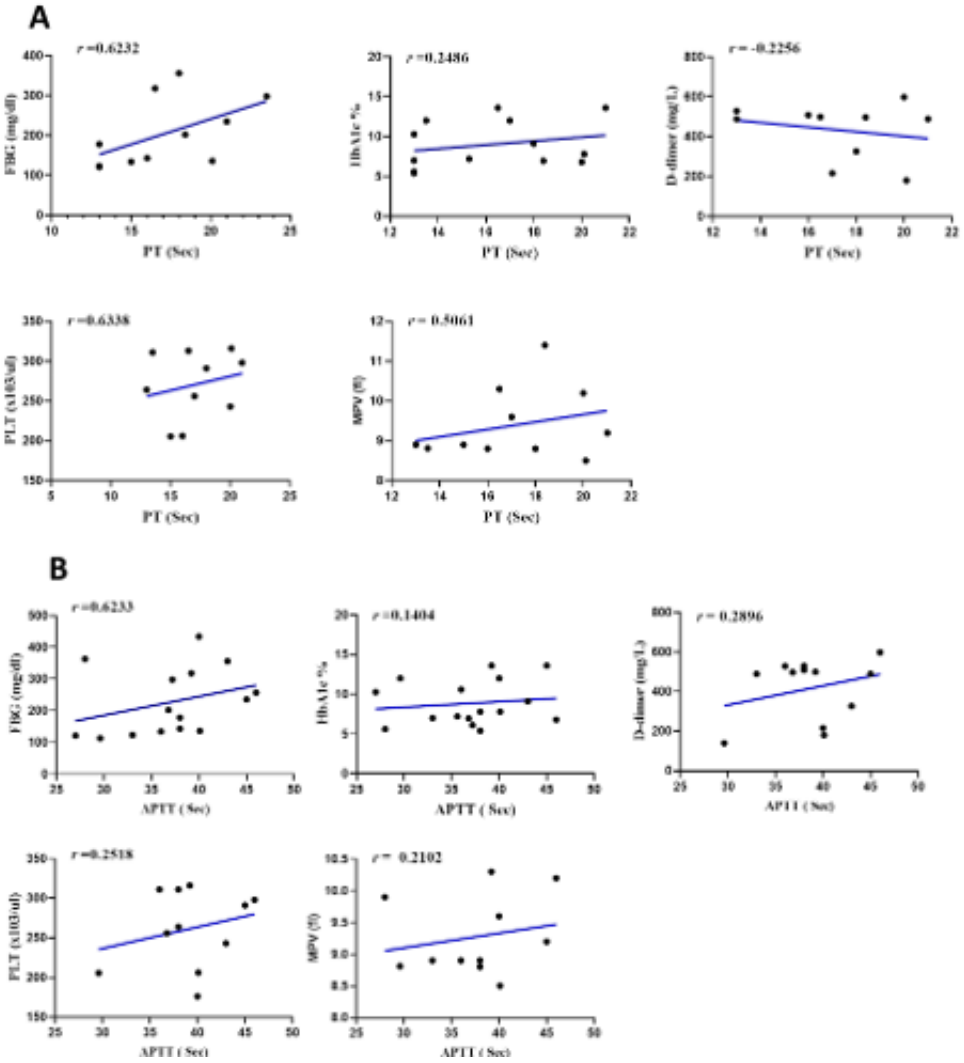


Figure 1. *Plot scatter showed the correlation coefficient between PT (sec) and physiological parameters (A), APTT (sec) and physiological parameters (B) of diabetic patients.*

Correlation between coagulation indicators and lipids profiles

Prothrombin time had a strong positive association with cholesterol and LDL levels of diabetic patients (r = 0.6523, p-0.032 and r = 0.6762, p-0.039). A weak positive relationship TG, HDL with prothrombin time in patients (r = 0.1799, p-0.538 and r = 0.2415, p-0.040). However, VLDL had a moderate negative association with prothrombin time (r = -0.4999, p-0.050). Data were appeared a moderate positive correlation prothrombin time value with AIP in diabetics patients (r = 0.5519, p- 0.048). A weak positive association was showed between prothrombin and TC/HDL ratio (r = 0.1467, p-0.616), Table (4) and Figure (2A)

A weak positive correlation was presented in table (4) between cholesterol, HDL and APTT value (r = 0.1235, p-0.661 and r = 3791, p-0.201). Conversely, APTT negatively associated with TG (r = - 0.3469, p-0.020). A strong positive association between APTT value and LDL in diabetic (r = 0.7961, p-0.007). However, VLDL and AIP presented a moderate negative association with APTT value (r = -0.4999, p-0.011 and r = - 0.5519, p-0.313). TC/HDL ratio presented a weak positive association with APTT value in patients group (r = 0.551, p-0.311), Table (4) and Figure (2B).

Parameters	PT (Sec)	P-value	APTT (Sec)
TC (mg/dl)	0.6523	*0.032	0.1235
TG (mg/dl)	0.1799	ns0.538	-0.3469
HDL (mg/dl)	0.2415	*0.040	0.3791
LDL (mg/dl)	0.6762	*0.039	0.7961

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

Academia Open
Vol 10 No 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10499 . Article type: (Medicine)

VLDL (mg/dl)	-0.4999	*0.050	-0.4835
AIP (mg/dl)	0.5519	*0.048	-0.4999
TC/HDL (mg/dl)	0.1467	ns0.616	0.5519

Table 4. *Pearson's correlation was analyzed between coagulation markers and lipids parameters of diabetes patients. Where ns p≥0.05, *p≤0.05.*

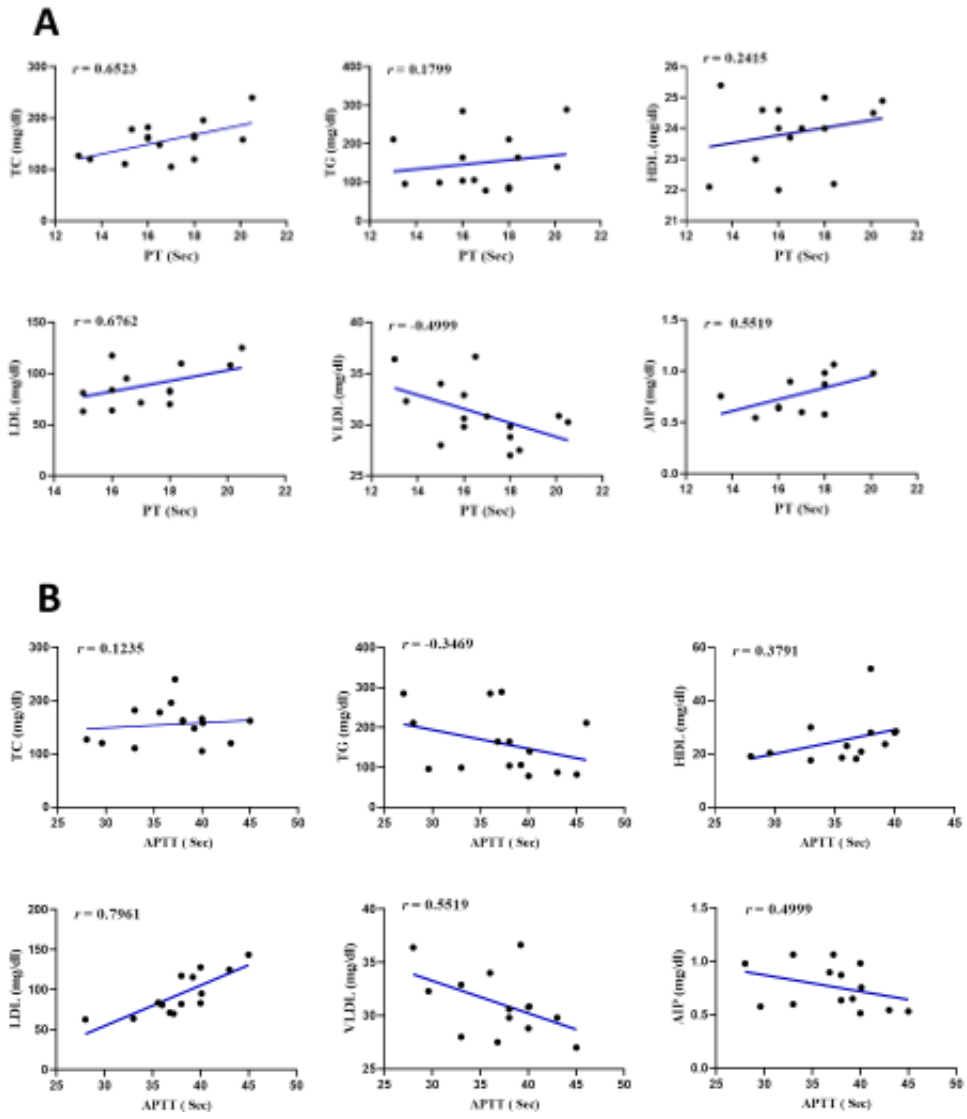


Figure 2. *Plot scatter showed the correlation coefficient between PT (sec) and lipid profiles (A), APTT (sec) and lipids profiles of diabetic patients.*

Discussion

Our findings observed a significant increase in lipid profile levels, while HDL levels were reduced in diabetic patients. Current data agree with other research's findings [33], [41]. They reported that lipid levels are related to cardiovascular diseases and diabetes mellitus. People suffering from diabetes often have high levels of TG, LDL, and low levels of HDL [64]. Diabetes plays a role in developing dyslipidemia by evaluating fatty acid release from insulin-resistant fat cells [43]. Insulin resistance has been associated with irregular lipid dysfunction in diabetes because resistance to insulin leads to increased fatty acid release, decreased fatty acid uptake by muscle, and elevated hepatic fatty acid production by the liver [8]. Free fatty acids could enhance triglycerides, which in turn prompt the release of apolipoprotein B and VLDL, increasing the risk of cardiovascular syndromes [43], [69]. High levels of triglycerides in patients with diabetes could stimulate VLDL levels, decrease HDL levels, and contribute to the high prevalence of cardiovascular diseases [43]. Hyperglycemia could negatively affect lipoproteins, including

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

VLDL and LDL, by raising oxidation and glycosylation, reducing vascular compliance, and promoting the development of atherosclerosis [27].

APTT, PT, and INR values of diabetic samples were significantly prolonged compared with healthy samples. These findings agree with results from other studies [57], [72]. Diabetic patients present symptoms of hypofibrinolysis and hypercoagulability. The increased values of PT, APTT, and INR could be due to increased endothelial wall impact, leading to sustained production of vasoactive substances that interfere with coagulation cascades [80]. Some studies found that coagulation indicators do not alter among diabetic patients [26], [50]. However, other studies claimed lower coagulation values in diabetic patients [6], [34]. These alterations in coagulation states are likely due to circulatory disturbances in patients, characterized by changes in coagulopathy, hemorheologic factors, altered endothelial metabolism, platelet activity, and fibrinolytic aberrations [46], [49]. Coagulation factors, including XII, VII, IX, I, and kallikrein, are elevated in diabetes mellitus, likely due to an imbalance of clotting factors with the endothelial surface [7]. Prolonged PT and APTT in diabetic cases imply that the intrinsic and extrinsic pathways are altered, potentially leading to extreme bleeding in case of injuries [12], [53]. Prolonged PT may result from a deficiency of clotting factor VII and cofactors I, II, and X or due to anticoagulant therapy [56]. PT and APTT are used to determine the extrinsic and intrinsic pathways of coagulation and identify bleeding or clotting tendencies. The significant prolongation of PT and APTT could result from hypercoagulable susceptibility due to an alteration of the thrombohemorrhagic balance favoring thrombosis in diabetic patients [18]. Increased PT could refer to FVII deficiency, while increased APTT suggests FXI or FVII decrease. The elongation of APTT and PT proposes deficiencies in FX, FII, fibrinogen, or FV aberrations. Increased APTT may occur due to liver dysfunction, as most coagulation factors are produced in the liver. Elevated PT and APTT values are associated with irregular coagulation mechanisms, suggesting a tendency for cardiovascular dysfunctions [40], [72]. Furthermore, increased values of these factors might be due to fibrin clot formation via inhibitors such as D-dimer and fragments of fibrinogen in diabetic subjects [72]. In diabetics, hyperglycemia is considered a major factor in promoting hypercoagulability, involving molecular mechanisms such as non-enzymatic glycation, increased oxidative stress, and decreased heparin sulfate [3].

D-dimer increased in the diabetes group compared with healthy controls. These data are consistent with previous investigations [10], [59]. The high D-dimer value could be due to oxidative stress and hyperglycemia over the period of diabetes mellitus [52]. The higher D-dimer value is a consequence of fibrin clot formation and its breakdown. Platelet count was elevated in patient specimens compared to the healthy group, in agreement with previous studies [81]. In diabetes, platelet hyperactivity occurs via endothelial vascular dysfunction due to inflammation, promoting vasoconstriction and increased production of cytokines and adhesion molecules that mediate platelet activation and adhesion to the endothelium [48]. Soares et al. found significant platelet values due to endothelial and platelet hypersensitivity, which could implicate endothelial dysfunction and vascular disorders [66]. This study observed an increase in MPV values in diabetic patients, consistent with Ragab et al., who documented an increase in MPV in diabetic patients [63]. MPV represents an indicator of thrombosis triggering and function. Larger platelets have increased thrombotic potential [21], [28].

Current work found that PT positively correlated with hyperglycemia index (FBG, HbA1c), PLT, and MPV, while PT negatively correlated with D-dimer. In addition, APTT has a positive relationship with all the criteria mentioned above. This data aligns with previous studies [18], [16], which noted a positive association between APTT, PT, and FBG in diabetics. Gopalakrishnan et al. reported a positive linear association between HbA1c and clotting markers (PT, APTT) [22]. Other studies found a negative correlation between coagulation indices and FBG among diabetic patients [16], [78]. Alao et al. showed no correlation between PT, APTT, and HbA1c [2]. This could result from hyperglycemia affecting hemostasis through chronic glucose exposure, leading to hemoglobin glycation and reduced production of coagulation factors [15], [65]. Increased glucose levels lead to insufficient activation of the intrinsic and extrinsic coagulation pathways [45]. Grant and Lemkes et al. indicated that hyperglycemia due to insulin resistance contributes to a thrombotic state by inducing fibrinolysis deficiency and activating coagulation [23], [42].

PT showed a positive correlation with lipid profiles, including TC, TG, HDL, LDL, AIP, and TC/HDL, while negatively associating with VLDL. Additionally, a positive correlation was observed between APTT and lipid profiles (TC, HDL, LDL, and TC/HDL), while APTT negatively correlated with TG, VLDL, and AIP. Morishita et al. demonstrated a strong association between coagulation factor levels and lipids, particularly triglyceride-rich lipoproteins [51]. Hiraga et al. found coagulation factors such as factor VII correlated with triglycerides [30]. Yang et al. reported that elevated TG increases blood viscosity, enhancing coagulation factor VII production, which is a risk factor for venous thrombosis [79]. TG levels have been shown to correlate with PAI-1 and factor VII levels [79]. High TG levels, reduced HDL, glucose intolerance, obesity, increased factor VII, decreased fibrinolytic capacity, and hyperinsulinemia are interconnected [74]. Alzghoul et al. highlighted the impact of hyperlipidemia on coagulation states [4]. Hyperlipidemia can contribute to coagulation abnormalities [17]. Lipid metabolism dysfunction is a primary cause of abnormal glucose levels, endothelial damage, and activation of blood coagulation pathways, leading to increased fibrinogen levels and a hypercoagulable state [1]. Endothelial damage, phospholipids from damaged tissue, and hemolysis can lead to intravascular coagulation [9], [32], [47].

Conclusion

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo

In conclusion, this study underscores the significant alterations in lipid profiles, coagulation parameters, and platelet activity in diabetic patients, highlighting their elevated risk for cardiovascular diseases and thrombotic events. The findings reveal a pronounced increase in triglycerides, LDL, and platelet count, alongside a decrease in HDL, which are in line with previous research. Furthermore, prolonged PT, APTT, and INR values suggest an altered coagulation cascade, likely due to endothelial dysfunction and insulin resistance. These changes are associated with hyperglycemia and dyslipidemia, reinforcing the need for early monitoring and intervention to manage coagulation and lipid abnormalities in diabetic individuals. The positive correlations between coagulation markers and lipid profiles indicate the intertwined relationship between metabolic disturbances and thrombotic risk, suggesting that targeting lipid metabolism may help reduce complications. Further research is needed to explore the underlying molecular mechanisms of these associations and evaluate potential therapeutic interventions, including those that address both coagulation and lipid imbalances in diabetes management.

References

1. . M. Ahmed, N. Chowdhury, G. Sofdar, S. Chakrovortty, M. Rahman, M. Aziz, and A. Rahman, "High fibrinogen level is an independent predictor of presence and severity of coronary artery disease," Cardiovascular Journal, vol. 7, pp. 4-10, 2014.
2. . O. Alao, D. Damulak, D. Joseph, and F. Puepet, "Haemostatic profile of patients with type 2 diabetes mellitus in Northern Nigeria," The Internet Journal of Endocrinology, vol. 6, pp. 1-4, 2009.
3. . S. Alzahrani and R. Ajjan, "Coagulation and fibrinolysis in diabetes," Diabetes and Vascular Disease Research, vol. 7, pp. 260-273, 2010.
4. . B. N. Alzghoul, R. Reddy, M. Chizinga, A. Innabi, B. Zou, E. S. Papierniak, and I. Faruqi, "Pulmonary embolism in acute asthma exacerbation: clinical characteristics, prediction model and hospital outcomes," Lung, vol. 198, pp. 661-669, 2020.
5. . D. J. Angiolillo, E. Bernardo, M. Sabaté, P. Jimenez-Quevedo, M. A. Costa, J. Palazuelos, R. Hernández-Antolin, R. Moreno, J. Escaned, and F. Alfonso, "Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease," Journal of the American College of Cardiology, vol. 50, pp. 1541-1547, 2007.
6. . B. Ankalayya, H. Sodhi, S. Modala, and M. Baghel, "A comparative study of coagulation time in type 2 diabetes mellitus and healthy individuals," International Journal of Contemporary Medical Research, vol. 3, pp. 3170-3171, 2016.
7. . B. A. Bashir and M. S. Ali, "Hemostatic state augmented with platelet indices among Sudanese diabetic septic foot," BMC Hematology, vol. 18, pp. 1-6, 2018.
8. . G. Boden, "Role of fatty acids in the pathogenesis of insulin resistance and NIDDM," Diabetes, vol. 46, pp. 3-10, 1997.
9. . W. F. Boron and E. L. Boulpaep, Medical Physiology E-book, Elsevier Health Sciences, 2016.
10. . A. H. Bryk, M. Konieczyńska, M. Polak, D. Plicner, M. Bochenek, and A. Undas, "Plasma fibrin clot properties and cardiovascular mortality in patients with type 2 diabetes: a long-term follow-up study," Cardiovascular Diabetology, vol. 20, pp. 1-11, 2021.
11. . M.E. Carr, "Diabetes mellitus: a hypercoagulable state," Journal of Diabetes and its Complications, vol. 15, pp. 44-54, 2001.
12. . P.K. Chaitanya, S. Kavuri, and K.A. Devi, "Comparison of prothrombin time and activated partial thromboplastin time between patients with diabetes mellitus and diabetics with hypertension," Int. J. Ph Bio Sci, vol. 5, pp. 705-709, 2014.
13. . R. Chilton, J. Wyatt, S. Nandish, R. Oliveros, and M. Lujan, "Cardiovascular comorbidities of type 2 diabetes mellitus: defining the potential of glucagonlike peptide–1-based therapies," The American Journal of Medicine, vol. 124, pp. S35-S53, 2011.
14. . M.A. Creager, T.F. Lüscher, F. Cosentino, and J.A. Beckman, "Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I," Circulation, vol. 108, pp. 1527-1532, 2003.
15. . M. Dallatu, P. Anaja, L. Bilbis, and F. Mojiminiyi, "Antioxidant micronutrient potentials in strengthening the antioxidant defense in alloxan-induced diabetic rats," Nigerian Journal of Pharmaceutical Sciences, vol. 8, pp. 89-94, 2010.
16. . H. Ebrahim, F. Asrie, and Z. Getaneh, "Basic coagulation profiles and platelet parameters among adult type 1 and type 2 diabetes patients at Dessie Referral Hospital, Northeast Ethiopia: comparative cross-sectional study," Journal of Blood Medicine, pp. 33-42, 2021.
17. . M.A. El Asrar, A. Adly, E.S. El Hadidy, and M.A. Abdelwahab, "D-dimer levels in type 1 and type 2 diabetic children and adolescents; Relation to microvascular complications and dyslipidemia—own data and review," Pediatric Endocrinology Reviews, vol. 9, pp. 657-668, 2012.
18. . J.K. Fadairo, A.D. Atere, T. Ogidiolu, and O. Abiodun, "Assessment of some coagulation indices among type II diabetic subjects in a tertiary facility in South West Region, Nigeria," IOSR-JDMS, vol. 15, pp. 159-163, 2016.
19. . M.A. Fattah, M.H. Shaheen, and M.H. Mahfouz, "Disturbances of haemostasis in diabetes mellitus," Disease Markers, vol. 19, pp. 251-258, 2003.
20. . Federation ID, Diabetes Atlas, 6th ed., ISND 2-930229-85-3, 2013. Online version of IDF Diabetes Atlas: www.idf.org.
21. . M. Gawaz, H. Langer, and A.E. May, "Platelets in inflammation and atherogenesis," The Journal of Clinical

Investigation, vol. 115, pp. 3378-3384, 2005.
22. . S. Gopalakrishnan, G. Anuradha, S. Sumathy, S. Unnikrishnan, and S. Dhanvarshini, "Study to evaluate the correlation between coagulation factor, glycemic control and the severity of diabetic foot ulcers among South Indian population: A case control study," Romanian Journal of Diabetes Nutrition and Metabolic Diseases, vol. 27, pp. 342-348, 2020.
23. . P. Grant, "Diabetes mellitus as a prothrombotic condition," Journal of Internal Medicine, vol. 262, pp. 157-172, 2007.
24. . K. Gündogan, F. Bayram, M. Capak, F. Tanriverdi, A. Karaman, A. Ozturk, H. Altunbas, C. Gökce, and A. Kalkan, "Prevalence of metabolic syndrome in the Mediterranean region of Turkey: evaluation of hypertension, diabetes mellitus, obesity, and dyslipidemia," Metabolic Syndrome and Related Disorders, vol. 7, pp. 427-434, 2009.
25. . V. Gyberg, D. De Bacquer, G. De Backer, C. Jennings, K. Kotseva, L. Mellbin, O. Schnell, J. Tuomilehto, D. Wood, and L. Rydén, "Patients with coronary artery disease and diabetes need improved management: a report from the EUROASPIRE IV survey: a registry from the EuroObservational Research Programme of the European Society of Cardiology," Cardiovascular Diabetology, vol. 14, pp. 1-11, 2015.
26. . S. J. Hamilton and G. F. Watts, "Endothelial dysfunction in diabetes: Pathogenesis, significance, and treatment," The Review of Diabetic Studies: RDS, vol. 10, pp. 133, 2013.
27. . Z. Hekimsoy, B. Payzin, T. Örnek, and G. Kandoğan, "Mean platelet volume in Type 2 diabetic patients," Journal of Diabetes and Its Complications, vol. 18, pp. 173-176, 2004.
28. . K. Hess, "The vulnerable blood," Hämostaseologie, vol. 35, pp. 25-33, 2015.
29. . T. Hiraga, M. Shimada, T. Tsukada, and T. Murase, "Hypertriglyceridemia, but not hypercholesterolemia, is associated with the alterations of fibrinolytic system," Hormone and Metabolic Research, vol. 28, pp. 603-606, 1996.
30. . S. Hörber, R. Lehmann, N. Stefan, J. Machann, A. Birkenfeld, R. Wagner, M. Heni, H. U. Häring, A. Fritsche, and A. Peter, "Hemostatic alterations linked to body fat distribution, fatty liver, and insulin resistance," Molecular Metabolism, vol. 53, p. 101262, 2021.
31. . L. Horn, W. Pao, D. Johnson, D. Longo, D. Kasper, J. Jamson, A. Fauci, S. Hauser, and J. Loscalzo, Harrison's Principles of Internal Medicine, 18th ed., McGraw-Hill, New York, 2012.
32. . H. Kaneko, H. Itoh, H. Kiriyama, T. Kamon, K. Fujiu, K. Morita, N. Michihata, T. Jo, N. Takeda, and H. Morita, "Lipid profile and subsequent cardiovascular disease among young adults aged <50 years," The American Journal of Cardiology, vol. 142, pp. 59-65, 2021.
33. . F. Karim, Q. S. Akter, S. Jahan, A. Khanom, S. Haque, T. Yeasmin, T. Siddika, and S. Sinha, "Coagulation impairment in type 2 diabetes mellitus," Journal of Bangladesh Society of Physiologists, vol. 10, pp. 26-29, 2015.
34. . D. M. Kendall and A. P. Harmel, "The metabolic syndrome, type 2 diabetes, and cardiovascular disease: Understanding the role of insulin resistance," American Journal of Managed Care, vol. 8, pp. S635-S653, 2002.
35. . H. Khan, S. Sobki, and S. Khan, "Association between glycaemic control and serum lipids profile in type 2 diabetic patients: HbA1c predicts dyslipidaemia," Clinical and Experimental Medicine, vol. 7, pp. 24-29, 2007.
36. . H. A. Khan and M. S. Ola, "Markers of blood coagulation, lipid profile, renal function test and serum electrolytes in streptozotocin-induced diabetic rats," Biomed Res-India, vol. 23, pp. 421-424, 2012.
37. . J. A. Kim, J. E. Kim, S. H. Song, and H. K. Kim, "Influence of blood lipids on global coagulation test results," Annals of Laboratory Medicine, vol. 35, pp. 15, 2015.
38. . J. H. Kim, H. Y. Bae, and S. Y. Kim, "Clinical marker of platelet hyperreactivity in diabetes mellitus," Diabetes & Metabolism Journal, vol. 37, pp. 423-428, 2013.
39. . M. A. Laffan and R. Manning, "Investigation of haemostasis," in Dacie and Lewis Practical Haematology, pp. 393-445, Elsevier, 2012.
40. . H. Lee, J. B. Park, I. C. Hwang, Y. E. Yoon, H. E. Park, S. Y. Choi, Y. J. Kim, G. Y. Cho, K. Han, and H. K. Kim, "Association of four lipid components with mortality, myocardial infarction, and stroke in statin-naïve young adults: A nationwide cohort study," European Journal of Preventive Cardiology, vol. 27, pp. 870-881, 2020.
41. . B. A. Lemkes, J. Hermanides, J. H. DeVries, F. Holleman, J. C. Meijers, and J. B. Hoekstra, "Hyperglycemia: A prothrombotic factor?" Journal of Thrombosis and Haemostasis, vol. 8, pp. 1663-1669, 2010.
42. . B. M. Leon and T. M. Maddox, "Diabetes and cardiovascular disease: Epidemiology, biological mechanisms, treatment recommendations, and future research," World Journal of Diabetes, vol. 6, pp. 1246, 2015.
43. . Z. Li, C. Qi, Z. Jia, R. Zhen, L. Ren, Y. Jia, and S. Chen, "The correlation between estimated glucose disposal rate and coagulation indexes in Type 2 diabetes mellitus," Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, pp. 2643-2652, 2022.
44. . G. Lippi, M. Franchini, G. Targher, M. Montagnana, G. L. Salvagno, G. C. Guidi, and E. J. Favaloro, "Epidemiological association between fasting plasma glucose and shortened APTT," Clinical Biochemistry, vol. 42, pp. 118-120, 2009.
45. . I. MacFarlane, "Endocrine diseases and diabetes mellitus," in Textbook of Diabetes, pp. 64.61-64.17, 1997.
46. . K. G. Mann, S. Butenas, and K. Brummel, "The dynamics of thrombin formation," Arteriosclerosis, Thrombosis, and Vascular Biology, vol. 23, pp. 17-25, 2003.
47. . P. Marchio, S. Guerra-Ojeda, J. M. Vila, M. J. Aldasoro, V. M. Victor, and M. D. Mauricio, "Targeting early atherosclerosis: A focus on oxidative stress and inflammation," Oxidative Medicine and Cellular Longevity,

vol. 2019, p. 8563845, 2019.
48. . I. Martín-Timón, C. Sevillano-Collantes, A. Segura-Galindo, and F. J. del Cañizo-Gómez, "Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength?" World Journal of Diabetes, vol. 5, pp. 444, 2014.
49. . H. Matcas, "Study on the anomalies of hemostasis on a group of dislipoproteinemia patients," Master's thesis, University of Medicine and Pharmacy, Craiova, 2009.
50. . E. Morishita, H. Jokaji, and T. Matsuda, "Hyperlipidemia and the hemostatic system," Journal of Atherosclerosis and Thrombosis, vol. 2, pp. S36-S40, 1995.
51. . N. A. Muhsin and S. S. Al-Mudallal, "Evaluation of plasma fibrinogen, D-dimer, and C-reactive protein as predictive parameters for coronary heart diseases in Type 2 diabetic patients," Mustansiriya Medical Journal, vol. 13, pp. 12, 2014.
52. . S. W. Mutua, "Evaluation of prothrombin time, international normalized ratio, and activated partial thromboplastin time tests in diabetes mellitus patients at Meru Teaching and Referral Hospital in Kenya," JKUAT-COHES, 2021.
53. . D. Mylotte, G. Kavanagh, A. Peace, A. Tedesco, D. Carmody, M. O'Reilly, D. Foley, C. Thompson, A. Agha, and D. Smith, "Platelet reactivity in Type 2 diabetes mellitus: A comparative analysis with survivors of myocardial infarction and the role of glycaemic control," Platelets, vol. 23, pp. 439-446, 2012.
54. . A. Ogedegbe, "An overview of hemostasis," Laboratory Medicine, vol. 33, pp. 948-953, 2002.
55. . M. O. Omare, J. K. Kibet, J. K. Cherutoi, and F. O. Kengara, "A review of tobacco abuse and its epidemiological consequences," Journal of Public Health, vol. 1, pp. 1-16, 2021.
56. . J. I. Osende, J. J. Badimon, V. Fuster, P. Herson, P. Rabito, R. Vidhun, A. Zaman, O. J. Rodriguez, E. I. Lev, and U. Rauch, "Blood thrombogenicity in Type 2 diabetes mellitus patients is associated with glycemic control," Journal of the American College of Cardiology, vol. 38, pp. 1307-1312, 2001.
57. . L. Pan, Y. Ye, M. Wo, D. Bao, F. Zhu, M. Cheng, X. Ni, and X. Fei, "Clinical significance of hemostatic parameters in the prediction for Type 2 diabetes mellitus and diabetic nephropathy," Disease Markers, vol. 2018, 2018.
58. . M. Pandya, C. Parmar, and M. Singh, "Study of prothrombin time and activated partial thromboplastin time in Type II diabetes mellitus," International Journal of Clinical and Diagnostic Pathology, vol. 3, pp. 173-175, 2020.
59. . M. Pawelczyk, B. Kaczorowska, and Z. Baj, "The impact of hyperglycemia and hyperlipidemia on plasma P-selectin and sCD40L concentrations in Type 2 diabetes mellitus," Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy, vol. 15, pp. 3355-3363, 2022.
60. . M. Pandya, C. Parmar, and M. Singh, "Study of Prothrombin Time and Activated Partial Thromboplastin Time in Type II Diabetes Mellitus," International Journal of Clinical and Diagnostic Pathology, vol. 3, pp. 173-175, 2020.
61. . M. Pawelczyk, B. Kaczorowska, and Z. Baj, "The Impact of Hyperglycemia and Hyperlipidemia on Plasma P-Selectin and Platelet Markers after Ischemic Stroke," Arch Med Sci, vol. 13, pp. 1049–1056, 2017.
62. . P. Poredos and M. K. Jezovnik, "Dyslipidemia, Statins, and Venous Thromboembolism," in Seminars in Thrombosis and Hemostasis, pp. 897-902, Thieme Medical Publishers, 2011.
63. . U. Ragab, F. O. Selim, A. I. El-Agroody, M. H. E. Mourad, and M. M. Sakr, "The Relationship of Mean Platelet Volume and Atherogenic Index of Plasma with Atherothrombotic Cardiovascular Disease in Diabetes," Romanian Journal of Diabetes Nutrition and Metabolic Diseases, vol. 27, pp. 112-119, 2020.
64. . H. S. Al-Shaheeb, K. Hashim, A. K. Mohammed, H. A. Almashhadani, and A. Al Fandi, "Assessment of Lipid Profile with HbA1c in Type 2 Diabetic Iraqi Patients," Revis Bionatura, vol. 7, pp. 29, 2022.
65. . E. Selvin, M. W. Steffes, H. Zhu, K. Matsushita, L. Wagenknecht, J. Pankow, J. Coresh, and F. L. Brancati, "Glycated Hemoglobin, Diabetes, and Cardiovascular Risk in Nondiabetic Adults," New England Journal of Medicine, vol. 362, pp. 800-811, 2010.
66. . A. L. Soares, M. d. O. Sousa, A. P. S. M. Fernandes, and M. d. G. Carvalho, "Hemostatic Changes in Patients with Type 2 Diabetes Mellitus," Revista Brasileira de Hematologia e Hemoterapia, vol. 32, pp. 482-488, 2010.
67. . A. I. Sobczak and A. J. Stewart, "Coagulatory Defects in Type-1 and Type-2 Diabetes," International Journal of Molecular Sciences, vol. 20, p. 6345, 2019.
68. . S. S. Soedamah-Muthu, N. Chaturvedi, M. Toeller, B. Ferriss, P. Reboldi, G. Michel, C. Manes, J. H. Fuller, and the EURODIAB Prospective Complications Study Group, "Risk Factors for Coronary Heart Disease in Type 1 Diabetic Patients in Europe: The EURODIAB Prospective Complications Study," Diabetes Care, vol. 27, pp. 530-537, 2004.
69. . M. P. Solano and R. B. Goldberg, "Management of Dyslipidemia in Diabetes," Cardiology in Review, vol. 14, pp. 125-135, 2006.
70. . J. Stamler, O. Vaccaro, J. D. Neaton, D. Wentworth, and the MRFIT Study Group, "Diabetes, Other Risk Factors, and 12-Year Cardiovascular Mortality for Men Screened in the Multiple Risk Factor Intervention Trial," Diabetes Care, vol. 16, pp. 434-444, 1993.
71. . Y. Takada, T. Urano, I. Watanabe, A. Taminato, T. Yoshimi, and A. Takada, "Changes in Fibrinolytic Parameters in Male Patients with Type 2 (Non-Insulin-Dependent) Diabetes Mellitus," Thrombosis Research, vol. 71, pp. 405-415, 1993.
72. . S. Thukral, S. Hussain, S. Bhat, N. Kaur, and A. Reddy, "Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) in Type 2 Diabetes Mellitus: A Case Control Study," International Journal of Contemporary Medical Research, vol. 5, pp. H5-H9, 2018.
73. . K. T. Tonks, C. P. White, J. R. Center, D. Samocha-Bonet, and J. R. Greenfield, "Bone Turnover is

Suppressed in Insulin Resistance, Independent of Adiposity," The Journal of Clinical Endocrinology & Metabolism, vol. 102, pp. 1112-1121, 2017.
74. . D. Toussoules, G. Davies, J. Ambrose, S. C. Tentolouris, and P. Toutouzas, "Effects of Lipids on Thrombotic Mechanisms in Atherosclerosis," International Journal of Cardiology, vol. 86, pp. 239-247, 2002.
75. . A. Undas, I. Wiek, E. Stêpien, K. Zmudka, and W. Tracz, "Hyperglycemia is Associated with Enhanced Thrombin Formation, Platelet Activation, and Fibrin Clot Resistance to Lysis in Patients with Acute Coronary Syndrome," Diabetes Care, vol. 31, pp. 1590-1595, 2008.
76. . V. R. Vaidyula, A. K. Rao, M. Mozzoli, C. Homko, P. Cheung, and G. Boden, "Effects of Hyperglycemia and Hyperinsulinemia on Circulating Tissue Factor Procoagulant Activity and Platelet CD40 Ligand," Diabetes, vol. 55, pp. 202-208, 2006.
77. . H. Wada, Y. Mori, T. Kaneko, Y. Wakita, K. Minamikawa, M. Ohiwa, S. Tamaki, N. Yokoyama, T. Kobayashi, and K. Deguchi, "Hypercoagulable State in Patients with Hypercholesterolemia: Effects of Pravastatin," Clinical Therapeutics, vol. 14, pp. 829-834, 1992.
78. . X. C. Xiangyu, F. Le, H. L. Hongbo, S. Peng, T. Zhang, L. Hui, L. Xiaoyong, Y. Min, X. Chunxiao, and J. Zhang, "The Relationship between Type 2 Diabetes and Platelet Indicators," Iranian Journal of Public Health, vol. 46, pp. 1211, 2017.
79. . W. Yang, S. Ren, and J. Liang, "Application and Effect of High-Quality Nursing Combined with Enteral Nutrition Support in Patients with Acute Pancreatitis," J. Mod. Nurs. Pract. Res., vol. 1, pp. 1, 2021.
80. . A. Zaidi and L. Green, "Physiology of Haemostasis," Anaesthesia & Intensive Care Medicine, vol. 20, pp. 152-158, 2019.
81. . Y. Zhang, R. Chen, Y. Jia, M. Chen, and Z. Shuai, "Effects of Exenatide on Coagulation and Platelet Aggregation in Patients with Type 2 Diabetes," Drug Design, Development and Therapy, pp. 3027-3040, 2021.

ISSN 2714-7444 (online), https://acopen.umsida.ac.id, published by Universitas Muhammadiyah Sidoarjo