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ORIGINAL ARTICLE

Effect of Deuterated Aspirin Treatment of Obese Iraqi Patients With Blood Hyperviscosity Syndrome

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Abstract

Background/Aim: Hyperviscosity syndrome (HVS) is a predictor of blood flow resistance and blood viscosity, density or thickness. A number of factors that influence blood viscosity have been identified. This study aimed to compare the effects of the deuterated aspirin (aspirin-D) to standard aspirin (aspirin-H) on the prothrombin time (PT) and the normalised international ratio (INR) in obese HVS patients and healthy individuals of normal weight. Haematocrit (HCT) was the primary determinant of blood viscosity and flow resistance.

Methods: The study included 120 Iraqi individuals, aged between 21 and 55 years, divided into 2 groups, 60 patients in an obese HVS group and 60 in a healthy weight control group. Total complete blood count, haemoglobin (Hb), the effects of aspirin-H and aspirin-D on blood viscosity were evaluated by measuring HCT, red blood cell (RBC), PT and INR.

Results: Patients aged 31–41 years with a body mass index (BMI) of 30–39.9 kg/m^2 constituted the largest proportion of the HVS group (41.66 %), while the same age group represented the highest percentage among healthy controls (40 %). Patients with HVS showed highly significant increases ($p < 0.001$) in anthropometric and haematological parameters, including BMI, Hb, HCT and RBC, along with a significant reduction in PT and INR compared to controls. Aspirin treatment, particularly deuterated aspirin, significantly increased PT and INR values, indicating improved anticoagulant activity.

Conclusion: Aspirin-D was superior to standard aspirin-H in reducing blood viscosity and delaying clotting time in both HVS patients and healthy subjects.

Key words: Aspirin; Blood viscosity; Deuteration; Hydrogen/Deuterium exchange; Hyperviscosity syndrome.

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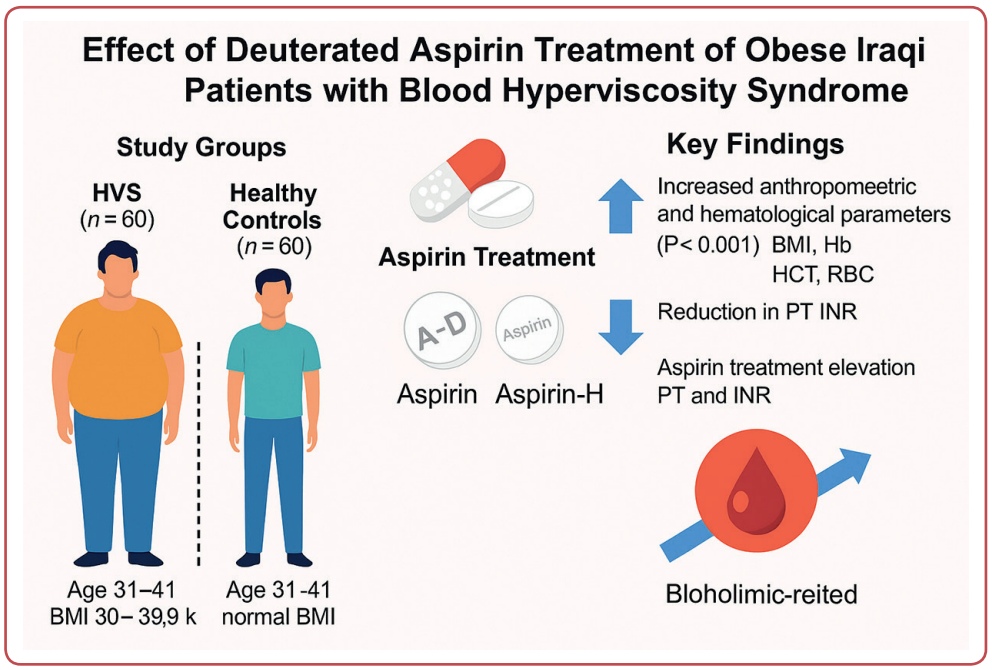

Graphical abstract

Introduction

Hyperviscosity syndrome (HVS) is a predictor of blood flow resistance and blood viscosity, density, or thickness.[1] A number of factors that influence blood viscosity have been identified, including the deformability of red blood cell (RBC), packed cell volume (haematocrit - HCT) and plasma viscosity. HCT is the major determinant. When HCT rises, as in erythrocytosis, the viscosity of blood can reach 10-fold higher than that of water.[2] HVS develops in various haematological diseases, such as leukaemia, sickle cell anaemia, Waldenström macroglobulinaemia (WM) and multiple myeloma (MM).[3] When blood viscosity rises above the typical threshold of 4.0 cP, HVS appears.[4]

Patients with HVS experience various symptoms due to poor blood flow, containing headache, confusion, blurred vision, dizziness and thrombotic episodes with and without mucocutaneous haemorrhage.[3] High blood viscosity also arises as a result of either a deformation in the shape of RBCs or an abnormal increase in blood proteins, RBC, white bloods cells (WBC) and platelets,[5] or may also result from conditions such as dehydration, smoking, polycythaemia vera and high altitude living. Increased erythropoietin hormone synthesis is the cause of the overproduction of RBC.[6] The kidneys generate the glycoprotein hormone erythropoietin (EPO), which has 165 amino acids and stimulates the marrow in the bones to create erythrocytes.[7] EPO is composed of about 60 % protein and 40 % carbohydrate.[8]

Many antithrombotic drugs are used to avoid complications of HVS, including anticoagulants such as warfarin,[9] dabigatran,[10] rivaroxaban,[11] apixaban,[12] edoxaban,[13] heparin[14] and antiplatelet (anti-aggregation) agents such as aspirin.[15] Low-dose pharmaceutical blood thinners like warfarin sodium come in clathrate or amorphous forms.[9] Dabigatran etexilate is licensed in Europe and America for stroke prevention and embolism and for the treatment of deep vein thrombosis.[1]

Aspirin (ASA) is a nonsteroidal anti-inflammatory medication (NSAID) recognised for its efficacy in alleviating pain and inflammation. Aspirin, introduced in 1899, became the inaugural effective treatment for rheumatic diseases.[16] It is extensively utilised for the prophylaxis and management of atherosclerotic cardiovascular illnesses[15] and arterial thrombotic disorders owing to its anticoagulant qualities and efficacy in diminishing clot formation resulting from platelet aggregation. Aspirin also helps prevent stroke or other blood vessel diseases.[17] It has been observed that aspirin is effective in preventing or reducing the synthesis of thromboxane

A-2 (TXA2) in platelets. Mechanistically, aspirin blocks the formation of thromboxane through acetylserine situated in the active site of cyclooxygenase-1 (COX-1). Inhibition of COX-1 results in diminished TXA2 synthesis, an enzyme that enhances platelet formation, facilitates platelet aggregation and serves as a positive feedback mechanism during platelet activation.[18]

Hydrogen/deuterium (H/D) isotope exchange is a chemical process wherein hydrogen atoms are substituted with deuterium, or the reverse.[19] The reaction attracted significant interest in the 1960s and 1970s[20] and, by the end of the century, there was a great demand for D-labelled compounds, mainly for studies of kinetic isotope effects, chemical reaction mechanisms, the determination of enzyme mechanisms and the improvement of certain drugs.[21]

Isotope-labelled compounds are used in many industries, not least in the pharmaceutical sector. The incorporation of isotopes in an organic chemical reaction can affect the number and profile of products formed. A chemical reaction involving an isotope-containing species is subject to an isotope effect, or an increase or decrease in rate. Sigma bonds with a heavier isotope are shorter and stronger and have a lower zero-point vibrational energy. These properties are especially significant when isotopes are incorporated into drugs. The replacement of one H atom in a molecule with a larger and heavier D atom can affect the metabolic behaviour of a drug. The carbon-D bond is shorter and stronger than carbon-H, slowing metabolic degradation 6–10-fold. Therefore, H/D exchange can extend the half-life of a drug's efficacy while enhancing the patient's tolerance to it.[22] The mechanism of H/D exchange for an aromatic ring is shown in Figure 1.

HVS is an index of blood flow resistance and can also be described as the blood viscosity, mass, or thickness. HCT is a measure of the RBC content of the blood and is the major determinant of blood viscosity. Several antithrombotic agents, including aspirin, have been used in HVS treatment. H/D exchange can confer many metabolic benefits to a drug. According to authors' knowledge, all previous HVS research has concentrated on the impacts of aspirin-H and this is the first to investigate the effects of aspirin-D on blood viscosity. Hypothesis was that deuteration of aspirin, as an anticoagulant medicine, would improve the drug pharmacokinetics and reduce its side effects.

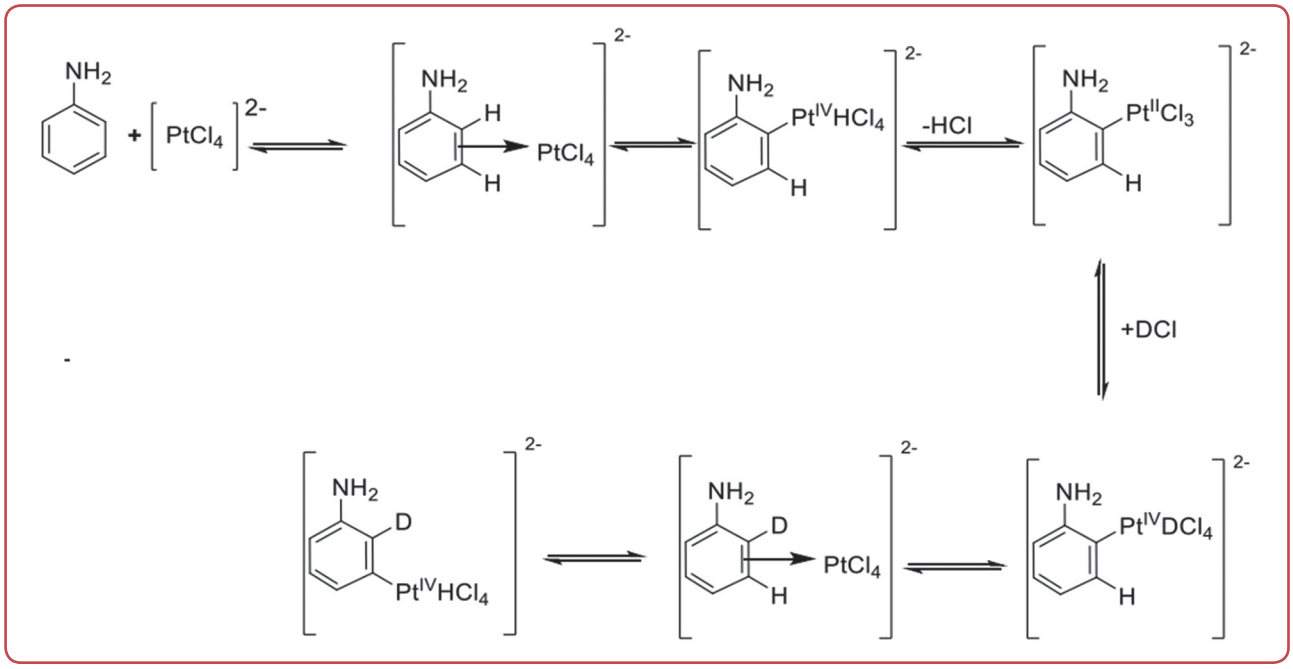

Figure 1: The hydrogen/deuterium (H/D) exchange reaction of an aromatic ring

Figure used with permission of author Dr Hussein Inayah Sharhan[22]

Methods

Study population

This research was carried out at Al-Imamian Al-Kadhimiyin City Hospital and Al-Thuraya laboratory from January 2024 to April 2024. The study comprised 120 Iraqi individuals aged between 21 and 55 years, categorised into two groups: a patient group consisting of 60 individuals diagnosed with HVS and obesity and a healthy control group consisting of 60 individuals with no known health issues. Patients were diagnosed based on clinical biochemical laboratory tests. All patients with chronic diseases (eg angina, stroke, cardiovascular disease) and taking anticoagulant medications and those with cancer, were excluded. The research work was conducted in compliance with the ethical principles for medical research and met the requirements of the Helsinki Declaration.

Specimen collection

Venous blood (5 mL) from each individual was drawn and collected in sodium citrate anticoagulant tubes. After collecting the blood sample and placing it on a roller mixer, it was stored in a refrigerator at 4 °C until use. The blood was then divided into 200 microliter aliquots in three 1.5 mL Eppendorf tubes. Blood samples were used for laboratory tests within 24 h of collection to avoid changes in their composition.[23] The blood was kept at 37 °C during analysis.[24]

Instruments and materials

The instruments used in this study included a centrifuge (Beckman model TJ-6, Germany), a roller mixer (model VM-370B, *Abbott,* Taiwan), a STart Max auto coagulation analyser (*Stago*, France), a Cell-Dyn Ruby automatic haematology analyser (*Abbott*, USA) and an incubator (*Yamato*, Japan).

The laboratory chemicals used in this study included haemoglobin (Hb), HCT and RBC kits (*Cell-Dyn Ruby*, USA). The kit for determination of prothrombin time (PT) and international normalised ratio (INR) was obtained from *Stago* (France). The PT and INR kit includes lyophilised thromboplastin (R1) and aqueous solvent containing calcium (R2). Aspirin-D (acetylsalicylic acid-D) was synthesised using the H/D exchange method of a previous study.[25]

Bio-clinical parameters

The sick and control persons were subsequently categorised into two subgroups based on their body mass index (BMI), calculated using the formula: BMI = weight (kg) / height (m^2).[26] Control healthy persons possess a BMI ranging from 19.9 to 24.9 kg/m^2, whereas HVS sufferers exhibit a BMI of 30 kg/m^2 or above. Complete blood counts (CBC), encompassing Hb, HCT and RBC levels, were analysed. The total viscosity was assessed utilising the PT and the international normalised ratio (INR) methodologies in plasma. Anthropometric measures were conducted for both groups.

The lipid accumulation product (LAP) was calculated using the formula: LAP (male) = [waist circumference (WC) (cm) – 65] × triglycerides (TG) (mmol/L).[27]

The visceral adiposity index (VAI) was calculated using the formula: VAI (male) = [WC(cm) / (39.68 + 1.88·BMI)] × (TG/1.03) × (1.31/ high-density lipoprotein cholesterol - HDL-C), with both TG and HDL levels measured in mmol/L.[28]

The waist-height ratio (WHtR) was calculated using the formula: WHtR = waist (cm) / height (cm) and the waist-hip ratio (WHpR) was calculated using the formula: WHpR = waist (cm) / hip (cm). The existence or non-existence of a familial history of HVS was also documented.

Comparative effect of aspirin (H/D) on PT and INR

The optimum conditions for aspirin administration, including concentration (0.03 M), temperature (37 °C) and incubation time (10 min), were determined in a previous study still in the publication process. Three sets of Eppendorf tubes containing 200 µL of whole blood were prepared. In the first set, the values of PT and INR were analysed without adding aspirin. In the second and third sets of blood tubes, the effects of aspirin-H and aspirin-D were assessed under the optimum conditions, whereby aspirin-H (0.03 M) and aspirin-D (0.01 M) were added to the blood and the samples were mixed using a rotary mixer. The blood samples in the second set were incubated with aspirin-H for 10 min at 37 °C in a digital incubator, while no incubation was required in the third set with aspirin-D. Then, the samples in the three sets were centrifuged for 15 min at 2500 rpm. Plasma samples (50 µL) were incubated for 50 s, then the PT and INR reagents (R1 + R2, 100 µL) were added and the values of PT and INR were measured in the three sets.

Calculations

The percentage effects of aspirin-H and aspirin-D on PT and INR were determined using the following equations:

% effect of aspirin-H = (PT(A) - PT(H))/PT(A) × 100

% effect of aspirin-D = (PT(A) - PT(D))/PT(A) × 100

where PT(A), PT(H) and PT(D) are the sample prothrombin times without aspirin, with aspirin-H and with aspirin-D, respectively. Similar equations were used for the corresponding INR(A), INR(H) and INR(D) values.

Statistical analysis

The results were statistically analysed utilising the Statistical Package with the Social Sciences (SPSS) on Windows version 26.0 (*IBM Corp*, Armonk, New York, USA). Values are shown as mean ± standard deviation (SD); a p-value beyond 0.05 was deemed non-significant, below 0.05 was regarded as significant and below 0.01 was classified as very significant. The t-test for paired samples was employed to compare mean values.

Results

The participants' demographic characteristics are displayed in Table 1. A non-significant variation ($p > 0.05$) was seen in the mean age of the HVS patients (36.65 ± 9.56) and that of the healthy control group (35.01 ± 9.13). The mean weight was highly significantly higher ($p < 0.001$) in HVS patients (93.41 ± 15.86 kg) than in the control group (75.46 ± 4.74 kg). The average height exhibited a statistically significant variance ($p < 0.01$) among the HVS patients (1.77 ± 0.07 cm) and the controls (1.81 ± 0.06 cm). The mean BMI was also highly significantly higher in HVS patients ($p < 0.001$) (32.90 ± 2.30 kg/m^2) in comparison with the controls (23.13 ± 1.09 kg/m^2).

Regarding the WHtR, a highly significant increase ($p < 0.001$) was observed in the HVS patients (0.60 ± 0.06) compared to the control group (0.40 ± 0.02) and the difference in WHpR (0.96 ± 0.13 vs 0.81 ± 0.04; $p < 0.001$) was equally significant. The VAI and LAP were also significantly higher in the patient group (4.40 ± 2.71 and 115.70 ± 56.76, respectively) compared to control group (2.82 ± 1.41 and 22.30 ± 14.69, respectively). A family history of HVS was recorded for 21.66 % of the HVS patients.

The distribution of BMI in patients with HVS (BMI 30–39.9 kg/m^2) and the control group (BMI 19.9–24.9 kg/m^2) across various age groups (21–55 years) is illustrated in Figure 2. In the group aged 21–31 years, 11 patients had HVS (18.33 % of the BMI distribution) and 21 represented the control group (35 % of the BMI distribution). The group aged 31–41 years represented 25 HVS patients (41.66 %) and 24 control (40 %) and the group ≥ 41 years represented 24 HVS patients (40 %) and 15 control (25 %).

Table 1: Anthropometric indices in hyperviscosity syndrome (HVS) patients and control group

Parameter	C1 Mean ± SD	G1 Mean ± SD	p-value
Age	35.01 ± 9.13	36.65 ± 9.56	0.330
Weight (kg)	75.46 ± 4.74	93.41 ± 15.86	< 0.001**
Height (m)	1.81 ± 0.06	1.77 ± 0.07	0.005**
BMI (kg/m^2)	23.13 ± 1.09	32.90 ± 2.30	< 0.001**
WHtR (cm/cm)	0.40 ± 0.02	0.60 ± 0.06	< 0.001**
WHpR (cm/cm)	0.81 ± 0.04	0.96 ± 0.13	< 0.001**
VAI	2.82 ± 1.41	4.40 ± 2.71	< 0.001**
LAP	22.30 ± 14.69	115.70 ± 56.76	< 0.001**
Family history (yes, no) %	-	21.66, 78.34 %	-

C1: control group of healthy individuals with normal BMI 19.9–24.9 kg/m^2; G1: obese HVS patients with BMI ≥ 30 kg/m^2; BMI: body mass index; WHtR: waist-height ratio; WHpR: waist-hip ratio; VAI: visceral adiposity index; LAP: lipid accumulation product; VAI (male) = [waist circumference (WC)(cm) / (39.68 + 1.88·BMI)] × (triglycerides (TG)/1.03) × (1.31/high-density lipoprotein cholesterol - HDL-C), (HDL in mmol/L); LAP (male) = (WC(cm) – 65) × TG, (TG in mmol/L); (*): significant p < 0.05; (**): highly significant p < 0.01;

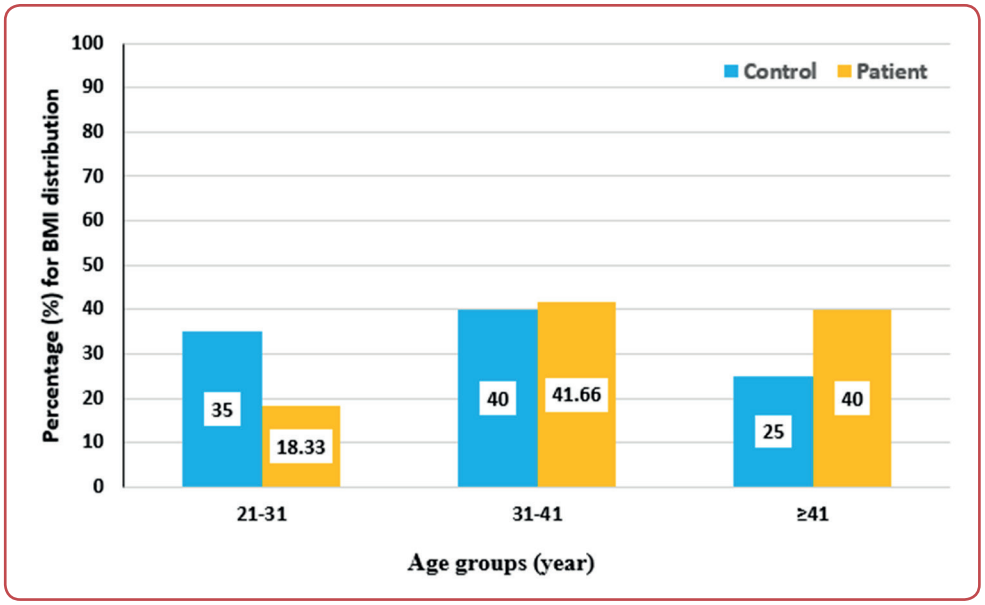

Figure 2: Distribution of body mass index (BMI) in hyperviscosity syndrome (HVS) patients and control group according to age

Complete blood counts for both groups are shown in Table 2. A highly significant increase ($p < 0.001$) was observed in the level of HCT in the HVS patient group (51.03 ± 1.79 %) compared to the control group (43.82 ± 1.64 %). The elevation of Hb (g/dL) and RBC (106/µL) in the patient group (17.4 ± 0.66 and 5.78 ± 0.36, respectively) was highly significant ($p < 0.001$) compared to the control group (14.96 ± 0.85 and 5.08 ± 0.26, respectively).

The values of PT and INR were measured in the absence and presence of aspirin-H and aspirin-D (Table 3). The results indicate a highly significant decrease ($p < 0.001$) in the mean plasma PT in the HVS patient group (12.86 ± 0.59 s) compared to the control group (14.23 ± 0.93 s). In the presence of aspirin-H, the mean plasma PT showed significant elevation ($p < 0.05$) in the HVS patient group (16.24 ± 1.31 s) compared with the control group (15.78 ± 1.11 s). In the presence of aspirin-D, the mean plasma PT exhibited a highly significant elevation (17.01 ± 1.75 s vs 16.28 ± 1.20 s for patient and control groups, respectively; $p < 0.01$). INR values were significantly decreased ($p < 0.01$) in the HVS patient group (0.95 ± 0.13) compared to the control (1.08 ± 0.26). In the presence of aspirin-H, the INR showed significant elevation ($p < 0.05$) in the HVS patient group (2.57 ± 1.35) compared to the control (2.18 ± 0.84). In the presence of aspirin-D, a similar trend was observed (3.39 ± 1.67 vs 2.73 ± 1.03; $p < 0.05$).

The impact of aspirin-D on blood viscosity in HVS patients is detailed in Table 4. Prior to adding aspirin-H or aspirin-D, the PT and INR were 12.86 seconds and 0.95, respectively. Upon adding aspirin-H, an increase in PT and INR was observed,

Table 2: Complete blood counts in the obese hyperviscosity syndrome (HVS) patient and control groups

Blood parameters	C1 Mean ± SD	G1 Mean ± SD	p-value
Hb (g/dL)	14.96 ± 0.85	17.4 ± 0.66	< 0.001**
HCT (%)	43.82 ± 1.64	51.03 ± 1.79	< 0.001**
RBC (10^6/UL)	5.08 ± 0.26	5.78 ± 0.36	< 0.001**

C1: control group of healthy individuals with normal body mass index (BMI): 19.9–24.9 kg/m²; G1: obese HVS patients with BMI ≥30 kg/m²; Hb: haemoglobin; HCT: haematocrit; RBC: red blood cell (erythrocytes); (*): significant $p < 0.05$; (**): highly significant $p < 0.01$;

Table 3: Comparison of PT and INR values between obese hyperviscosity syndrome (HVS) patients and control group

Blood parameters	C1 Mean ± SD	G1 Mean ± SD	p-value
PT without aspirin (s)	14.23 ± 0.93	12.86 ± 0.59	< 0.001**
PT with aspirin-H (s)	15.78 ± 1.11	16.24 ± 1.31	0.040*
PT with aspirin-D (s)	16.28 ± 1.20	17.01 ± 1.75	0.007**
INR without aspirin	1.08 ± 0.26	0.95 ± 0.13	0.001**
INR with aspirin-H	2.18 ± 0.84	2.57 ± 1.35	0.040*
INR with aspirin-D	2.73 ± 1.03	3.39 ± 1.67	0.010**

C1: control group of healthy individuals with normal body mass index (BMI): 19.9–24.9 kg/m^2; G1: obese HVS patients with BMI ≥ 30 kg/m^2; PT: prothrombin time; INR: international normalised ratio; s: seconds; (*): significant p < 0.05; (**): highly significant p < 0.01;

Table 4: Effect of aspirin-H and aspirin-D on PT and INR in obese hyperviscosity syndrome (HVS) patients

G1 group	(A)	(H)	(D)	% effect aspirin-H	% effect aspirin-D
PT (s)	12.86	15.44	17.01	20.0	32.2
INR	0.95	1.99	3.39	109.4	256.8

Obese HVS patients with body mass index (BMI): ≥ 30 kg/m^2; PT(A), PT(H), PT(D): prothrombin time without aspirin, with aspirin-H and with aspirin-D; INR(A), INR(H), INR(D): international normalised ratio without aspirin, with aspirin-H and with aspirin-D;

reaching 15.44 seconds and 1.99, respectively, corresponding to a 20 % increase in PT and a 109.4 % increase in INR. Notably, when aspirin-D was added, an even greater increase in PT and INR was noted, reaching 17.01 seconds (32.2 % increase) and 3.39 (256.8 % increase), respectively.

Discussion

In this study, a group of Iraqis with and without obesity and HVS were examined to determine how aspirin-H and aspirin-D affected blood viscosity. BMI is one of the anthropometric metrics that have been proposed to detect and diagnose obesity.[29-31] Obesity is linked to chronic low-grade inflammation and contributes significantly to the development of chronic illnesses such heart disease and stroke.[32] Blood composition can be impacted by elevated inflammatory cytokine levels and inflammation can raise the synthesis of fibrinogen and other clotting factors, which raises blood viscosity.[33] A blood plasma protein called fibrinogen is essential to the clotting process. Obese people often have higher levels of fibrinogen, which can make blood more viscous.[34] Obesity often leads to dyslipidaemia (abnormal levels of lipids in the blood), including higher levels of cholesterol and triglycerides. These changes can influence blood viscosity directly and indirectly through interactions with other blood components[35] and obesity is frequently accompanied by insulin resistance and elevated insulin levels (hyperinsulinemia). Insulin resistance can lead to endothelial dysfunction, which can promote blood clotting and increase blood viscosity.[36]

The current study is consistent with that of Brun et al, who found an increase in WHpR in patients with HVS.[37] Additionally, in another previous study, subjects with a WHpR greater than 0.90 were shown to have higher blood viscosity than those with a WHpR less than 0.90.[38] A further anthropometric measurement proposed to identify and diagnose obesity is the WHtR. WHtR is a reliable indicator of the risk of obesity in both sexes because BMI does not give the distribution of total body fat.[39] Measures of central adiposity, including waist circumference (WC) as well as WHpR, have supplanted BMI in a number of clinical diagnostic criteria as more accurate markers of cardiovascular risk linked to obesity.[40] The distribution of fat in the upper

and lower bodies is taken into consideration by WHpR.[41] Children and adolescents are more likely to be obese and to have related metabolic risks, such as cardiovascular diseases, as a result of increased consumption of calorie-dense foods and sedentary lifestyles.[42] Recently, the WHtR has been proposed as an effective anthropometric indicator for assessing central adiposity associated with cardiovascular and vascular risk factors.[43]

The results of this investigation are in line with those of Zhu et al,[44] who found that patients with HVS had higher levels of LAP and VAI than a control group.[45] VAI and LAP are measures of the amount of fat accumulated in the organs.[46] An increase in visceral fat formation and abnormalities in lipid metabolism may be caused by insulin resistance, which in turn could contribute to increased VAI and LAP levels.[47] Dysregulation of adipocyte activity and lipid metabolism may result from chronic inflammation, a feature shared by HVS. Increased visceral fat deposition and altered lipid profiles may be outcomes of this imbalance.[48] Hormones including cortisol and adipokines may have an impact on lipid levels in HVS[49] and the buildup of visceral fat and lipids may be accelerated by hormonal abnormalities.[50]

Non-alcoholic fatty liver disease (NAFLD), which affects liver function, affects lipid metabolism and storage and is linked to elevated VAI and LAP levels.[50] Some lifestyle and nutritional factors, including obesity, insufficient physical exercise and bad eating habits, may exacerbate visceral fat and lipid buildup in patients with HVS.[48] Furthermore, there may also be a hereditary component that increases the propensity to exhibit abnormal lipid profiles and thus higher VAI and LAP levels, as well as to build visceral fat.[51]

The demographic analysis is illustrated in Table 1. Patients between the ages of 31 and 41 represented the largest percentage of patients with HVS (41.66 %) and a BMI between 30 and 39.9 kg/m^2, whereas patients between the ages of 21 and 31 had the lowest HVS rate of 18.33 %. On the other hand, the group aged 31–41 years represented the largest percentage (40 %) within the control group (BMI = 19.9–24.9 kg/m^2), although this proportion was lower than that of the HVS group. According to Figure 2, the control group's lowest proportion (25 %) was observed among those who were at least 41 years of age.

The findings presented in Table 2 are consistent with those of Visza et al.[52] Whole blood viscosity is a complex phenomenon determined by many variables associated with RBCs, with haematocrit considered the most important among them.[53] The haematocrit value, representing the percentage of blood volume comprised of RBCs, is the most influential intrinsic factor of blood viscosity and is closely associated with haemoglobin concentration.[54]

Results for HGB and RBC in this current study are consistent with those of Alkhaldy et al.[55] Viscosity primarily depends on the ability of blood cells to deform under circulatory flow.[56] RBCs represent the majority of blood cellular components, making the greatest contribution to viscosity.[57] Hyperviscosity can be caused by elevated haemoglobin levels,[58] which may result from various disorders. Polycythaemia vera, a bone marrow disorder, causes an excess of RBCs, which raises the total haemoglobin and, in turn, the blood's viscosity.[59]

Table 3 shows how aspirin-H and aspirin-D affect blood viscosity in terms both PT and the INR. Presented results on PT without the addition of aspirin are in line with the research done by Roshal et al.[60] One of the first laboratory tests for the coagulation system was the PT. It measures how long it takes for a fibrin clot to develop in platelet-poor plasma that has been stimulated with high tissue factor (TF) and anionic phospholipids at the ideal calcium concentration.[60] The PT test is frequently used to track thrombolytic therapy, preventative therapies and medication therapy. It is an essential laboratory technique for evaluating individuals with coagulation problems.[61]

Because aspirin permanently suppresses cyclooxygenase-1 (COX-1), less TA2 is produced, which in turn reduces platelet aggregation. However, as an antiplatelet agent (rather than an anticoagulant like warfarin), aspirin primarily affects platelet aggregation, with a more indirect effect on blood viscosity.[62]

A decreased INR in the HVS patient group was associated with increased HCT levels (Tables 2 and 3).[63] In addition, a difference in blood viscosity was noted between the control group (C1) and the patient group (G1) when taking aspirin-H. The differences in plasma INR levels between the obese HVS patient group and the control group were significant when taking standard aspirin-H and aspirin-D. This could be explained by several factors, including HVS, which alters blood flow and microcirculation, leading to changes in coagulation parameters and INR. The mean values of PT and INR are a clear indication that

aspirin-D reduced the viscosity and delayed the clotting time better than aspirin-H (Table 4).

These findings suggest that the addition of either aspirin-H or aspirin-D exerts an effect on PT and INR in patients with HVS. The highest percentage effect was observed in the presence of aspirin-D. Deuterated aspirin may be more effective than standard aspirin in reducing hyperviscosity and improving prothrombin time due to the effect of deuterium exchange on drug metabolism and activity. When deuterium is added, the metabolism of several medications that are broken down via hydrogen-carbon bond scission pathways is slowed down.[64] As a result of the kinetic isotope effect, a molecule's physical and chemical properties can be altered by the incorporation of deuterium. The carbon-D bond is more resistant to enzyme cleavage than the carbon-H bond. Therefore, the deuterated molecule may undergo slower metabolism[22] and the active drug can stay in the bloodstream for longer, increasing its therapeutic effects.[65] The enzyme cyclooxygenase (COX) is essential for the production of TA2, an agent that promotes platelet aggregation and aspirin blocks this enzyme irreversibly.[66] Deuterated aspirin has a longer half-life than regular aspirin, meaning it is active for a longer period in the body and may have longer-lasting effects on blood viscosity and clotting time, as well as a more sustained suppression of platelet function.[67]

Conclusion

The current study established that the high-risk factor for HVS is obesity with a BMI in excess of 30 kg/m^2. The findings showed that aspirin-H and aspirin-D were effective in decreasing viscosity and prolonging clotting time and that aspirin-D effected these changes to a greater extent. This is due to the higher carbon-deuterium bond strength, requiring more time for metabolism. The incorporation of deuterium into aspirin led to increased PT and INR. Hence, aspirin-D is a better candidate for controlling platelet aggregation than standard aspirin. Results showed that aspirin-D is superior to standard aspirin-H in reducing viscosity and delaying clotting time. The study findings warrant further clinical investigation and pharmaceutical development of aspirin-D.

Ethics

The research received approval from the Scientific and Ethical Committee at Mustansiriyah University, College of Science, Baghdad, under registration number 51, dated 11 January 2024 and by the Training and Human Development Centre at Baghdad Health Directorate Al-Karkh, Ministry of Health, Baghdad, Iraq, under registration number 17863, dated 7 April 2024.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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