

## EFFECTS OF LOW MOLECULAR WEIGHT AND UNFRACTIONATED HEPARIN ON LIPOPROTEIN LIPASE AND LIPID PROFILE IN HAEMODIALYSIS PATIENTS

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## ABSTRACT

**Introduction:** In haemodialysis patients, mortality from cardiovascular disease is much greater than in the general population. The current study aimed to evaluate the effects of two different types of heparin, low molecular weight heparins (LMWH) and high molecular weight heparin (HMWH), on lipid profile in patients undergoing haemodialysis.**Material & Methods:** A total of 60 patients on haemodialysis were selected from two main hospitals of Lahore, Pakistan and were divided into two major groups based on the type of heparin used. A 5 ml blood sample was taken from the dialysis machine to get the serum and was kept frozen at -20°C for analysis of total cholesterol, triglycerides, high-density lipoprotein, and low-density lipoprotein. Comparison of lipoprotein lipase activity between groups were evaluated by using the student t-test. A *P*-value of  $\leq 0.05$  was considered statistically significant.**Results:** Gender wise distribution of study population (n=60) was 67% (n=40) males and 33% (n=20) females. The age distribution of individuals varied from 39-43 years. Moreover, use of HMWH was high in males (73%) as compared to female (27%) with an average age of  $39 \pm 12$  years where duration of haemodialysis was  $4.44 \pm 2.83$ . A significant difference in LPL activity related to different times in all patients was observed. A clearer difference observed in case of LDL where LPL activity was markedly different in both groups. Our data showed that individuals using LMWH had less chances of dyslipidaemia as compared to those using HMWH.**Conclusion:** LMWH is a useful and safe anticoagulant during haemodialysis as compared to HMWH.**Key Words:** Lipoprotein Lipase, Heparin, Haemodialysis.

The authors declared no conflict of interest and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed substantially to the planning of research, question designing, data collection, data analysis and write-up of the article.

**This article may be cited as** Jan A, Jahan S, Aziz N, Khan SA, Asia, Zeb Z, Khan AA. Effects of low molecular weight and unfractionated heparin on lipoprotein lipase and lipid profile in haemodialysis patients. *Rehman J Health Sci.* 2021;3(1). 56-59

## INTRODUCTION

Cardiovascular disease is a leading cause of morbidity and mortality among dialysis patients and accounts for half or more of the deaths.<sup>1,2</sup> The increased risk of cardiovascular events in haemodialysis (HD) patients not only includes high blood pressure, diabetes mellitus, increased concentration of lipids in the blood, increased use of tobacco, and lack of physical activity but also included use of heparin and metabolic disturbances associated with renal dysfunction. Renal-associated risk factors are renal dyslipidaemia, increased lipoprotein A levels, increased homocysteine level in the blood, decreased albumin level in the blood, hemodynamic disturbance and anemia.<sup>3</sup> In the early 1960s, HD was started for treating renal failure patients and the risk of clotting in extracorporeal devices was reduced to a minimum by use of heparin.<sup>4</sup> The pharmacodynamics of unfractionated heparin (UFH) vary among patients.<sup>5</sup> Usually a loading dose of approximately 50 IU/Kg body weight, followed by infusion of 800-1500 IU/hr is recommended for routine anticoagulation.<sup>6</sup> During the past few years, various low molecular weight heparin (LMWH) is increasingly used for HD. The main advantage of these are their easy administration<sup>7</sup> and a reduced increase in lipoprotein lipase (LPL) activity, reflecting the decreased effect on lipoproteins as

compared to UFH.<sup>8</sup> In early study heparin was used as an initial bolus dose and then followed by continuous infusion.<sup>9</sup> As LMWH preparations have longer effects on anticoagulation,<sup>10</sup> a single bolus injection before dialysis is now recommended even in dialysis sessions of five hours.<sup>11</sup> Molecular weight of UHF varies between 5,100 and 29,900 Dalton.<sup>12</sup> Reticuloendothelial system is the most important system regarding the breakdown of UFH, however, small amount passes in the urine as such.<sup>10</sup> Average half-life of UFH is normally around 55 minutes and this may be prolonged in individuals with end-stage renal failure. Protamine can be used to neutralize the anticoagulant effects of UFH and is given in the form of slow intravenous (IV) infusion. Bleeding, dyslipidaemia and abnormal hepatic function tests are the most common complications associated with the use of UFH.<sup>12</sup>

For the last few years, several types of LMWH are used in hospitals. LMWH is composed of segments of UFH which are formed by de-polymerization methods. These segments usually have a molecular weight of 1,000-10,000 Dalton, with a mean of 4500-5000 Dalton.<sup>5,12</sup> When administered IV, LMWH has two times longer duration of action as anticoagulant than UHF.<sup>10</sup> LMWH unlike UFH is metabolized by kidneys.<sup>10,12</sup> In contrast

to UFH, the anticoagulant effects of LMWH cannot be reversed by the use of protamine. LMWH is less associated with bleeding complications as compared to UFH. The current study aimed to evaluate the effects of two different types of heparin that are LMWH and UFH also called high molecular weight heparin (HMWH) on lipid profile in haemodialysis patients.

#### MATERIAL AND METHODS

Study subjects (n=60) both males and females were divided into two main groups (A and B) based on types of heparin used and each main group was divided into two subgroups (I and II) based on age. The criteria for inclusion were patients on HD for at least two months. Patients with ischemic heart diseases, carcinomas, and lymphomas were excluded from the study. Patients from Sheikh Zayed Hospital were using HMWH and those from Mayo Hospital were using LMWH. All patients participated willingly with prior written consent to undergo tests and examinations. History of the patients, demographic information, and biochemical findings were recorded in the prescribed proforma.

A 5 ml whole blood sample was taken in disposable syringes from one of the ports of the dialysis machine and placed in a plastic tube and to clot properly and get serum after passing through centrifugation and clear serum obtained was placed in tubes and kept frozen at -20°C for analysis of total cholesterol (TC), triglycerides (TGs), High-density lipoprotein (HDL) and Low-density lipoprotein (LDL). This whole procedure was applicable for baseline (0 minutes, at pre-dialysis) and consequent levels (15, 30, 60, 120, 180 minutes of dialysis) of LPL and other lipid tests.

#### Statistical Analysis

Statistical analysis was done on SPSS 20.0. Data for age, duration since on HD, LPL, and lipid profile (Total cholesterol, Triglyceride, HDL cholesterol, LDL cholesterol) for various times during dialysis was described by using Mean  $\pm$  SD for both groups. A *p*-value of  $\leq 0.05$  was considered statistically significant.

#### RESULTS

Blood samples from 60 patients on haemodialysis were collected from two main hospitals in Lahore. Out of the total, according to gender distribution, 67% (n=40) individuals were males and 33% (n=20) were females (Table 1). Gender wise distribution of use of low molecular weight heparin (LMWH) was high in male (60%, n=18) individuals as compared to female (40%, n=12) with an average age of  $42 \pm 14$  years with a  $2.81 \pm 2.99$  duration of haemodialysis. Moreover, use of high molecular weight heparin (HMWH) was high in males (73%, n=22) as compared to female (27%, n=8) with an average age of  $39 \pm 12$  years with  $4.44 \pm 2.83$  duration of haemodialysis (Table 1). As far as whole study population was concerned, the use of LMWH and HMWH was equally distributed. Comparison of LPL activity between two main and two sub-groups was evaluated by using a student t-test. Based on statistical analysis there was a significant difference in LPL activity related to different times in all patients (Figures 1-4). More clear difference was observed in LDL where LPL activity was markedly different in both groups (Figure 4). In conclusion, results of the study showed that there were fewer chances of dyslipidaemia in individuals using LMWH as compared to those using UFH or HMWH.

#### DISCUSSION

In our study, the effects of heparin were determined between two main groups (A and B), there was a significant difference in LPL activity ( $P < 0.05$ ) with time except between 15-30 minutes. These findings are in close agreement with the study reported previously.<sup>13</sup> In the present study, the result of total cholesterol between the two main groups was statistically non-significant having a *p*-value  $> 0.05$  and such observations were seen in another study from Sweden.<sup>14</sup> Another study from Riyadh, Saudi Arabia, reported that fewer chances of dyslipidaemia occur with low molecular weight heparin.<sup>15</sup> Another study from Egypt<sup>16</sup> also recorded that as compared to unfractionated heparin, the low molecular weight was effective and found statistically significant. This study's findings are in agreement with the current study. The present study revealed that the levels of triglycerides were low from baseline to 60 minutes after giving LMWH and was statistically significant ( $P < 0.05$ ) in group A as compared to group B (receiving HMWH) where a decrease in triglyceride level was observed from baseline to 15 minutes and was significant ( $P < 0.05$ ). Similar results were observed in another study from Sweden reported previously<sup>14</sup> which support our current study findings.

In the current study, levels of HDL cholesterol (considered to be good lipoproteins) rises from baseline to 30 minutes ( $P < 0.05$ ) in group A receiving low LMWH patients while in group B patients there was no significant rise in HDL cholesterol, rather a fall in HDL cholesterol levels from 120 minutes to 180 minutes ( $P < 0.05$ ) was observed. These findings correlate with the findings of studies conducted previously.<sup>16</sup> In the present study, levels of LDL cholesterol (considered to be the bad lipoproteins) rises significantly ( $P < 0.05$ ) only from baseline to 15 minutes in group A patients receiving LMWH while LDL cholesterol level raised significantly ( $P < 0.05$ ) from baseline to 120 minutes. These findings were also observed in a previous study.<sup>14</sup> Previous study investigations from the USA<sup>17</sup> supports our current study findings as LMWH used safe in chronic haemodialysis patients. Another study from Iran reported that LMWH was an effective and safe anticoagulant for haemodialysis patients.<sup>18</sup> Same results were observed in this study and were supported by other previous studies.<sup>19, 20</sup>

Majority of the studies showed a decrease in lipid levels using LMWH except for three which reported either an increase or no changes for cholesterol,<sup>21,22</sup> LDL-cholesterol,<sup>21,23</sup> and triglycerides.<sup>22,23</sup> Findings of these studies are not similar to the current study findings. The European Best Practice Guidelines for haemodialysis recommended the use of LMWH yet another study reported that UFH remained the most frequent choice for treatment of haemodialysis patients in North America.<sup>24</sup> The cost may be the main argument for not using LMWH in haemodialysis and their safety remains a major concern. These findings are not similar to the current study, as the current study reported that LMWH is safe in haemodialysis patients. Both hepatic and renal pathways metabolized the UFH by but LMWH is mainly through kidneys leading to potential bioaccumulation and arises risk of haemorrhage.<sup>25</sup> Another study conducted by Lim et al. which reported

the efficacy and safety of LMWH in hemodialysis<sup>26</sup> had the same results as observed in the current study.

### CONCLUSION

Low molecular weight heparins (LMWH) are a better, useful, and safe anticoagulant for haemodialysis patients. LMWH has positive effects on HDL considered to be the best lipoprotein in the human body in contrast to LDL. Larger studies are needed to evaluate properly the safety of LMWH haemodialysis patients.

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Table.1 Gender, age and duration of Haemodialysis of patients using types of heparin

Types of heparin	Male	Female	Age	Duration of haemodialysis
Low molecular weight heparin	18	12	42±14	2.81±2.99
High molecular weight heparin	22	08	39±12	4.44±2.83

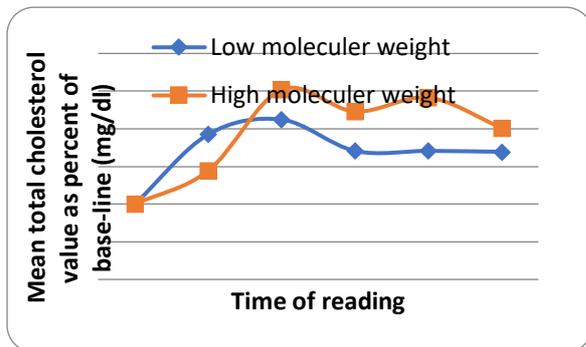


Figure.1: Pattern of total cholesterol with times after use of LMWH and HMWH

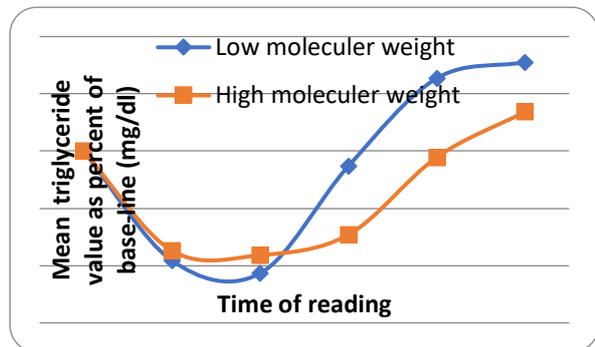


Figure.2: Pattern of triglycerides with times after use of LMWH and HMWH Statistically

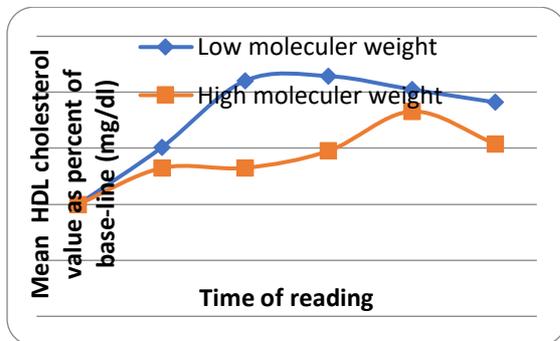


Figure.3:HDL with after use of LMWH and HMWH

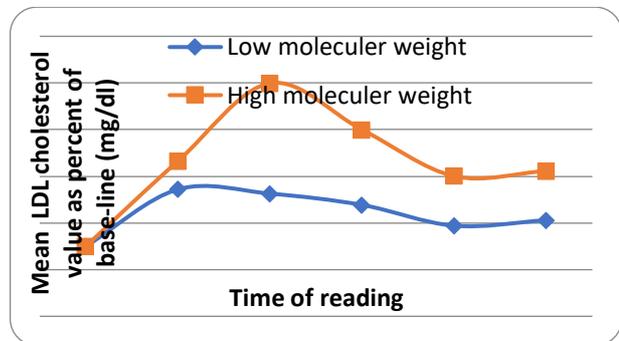


Figure.4: LDL with use of LMWH and HMWH