Prevalence of cardiovascular diseases and risk factors in adult patients with haemophilia: a cross-sectional study in a tertiary care hospital clinic in Sri Lanka

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Abstract
Background: Management of cardiovascular disease (CVD) in patients with haemophilia is extremely challenging. Therefore, knowing the prevalence of CVD and risk factors in this population is imperative.

Methods: All consented patients ≥ 18 years of age attending the haemophilia clinic at a tertiary care centre were recruited to the study. Data were collected using a pretested, investigator administered questionnaire. Seated blood pressure, anthropometric measurements and blood samples were obtained using standard techniques. Lipid profile and fasting plasma glucose were estimated. Prevalence of risk factors for CVD was compared with those of age matched males in the general population. P values < 0.05 were considered significant.

Results: Of the total 109 participants, 92 (84.4%) had haemophilia A. The median age of the study group was 36 years. Three (2.8%) had at least one cardiovascular disease. There were 10 (9.2%), 30 (27.5%), 13 (11.9%) and 4 (3.7%) participants with diabetes, hypertension, current smoking and obesity (Body Mass Index (BMI) ≥ 30 kg/m²) respectively. 32 (29.4%) and 37 (33.9%) participants had waist circumference ≥ 90 cm and waist hip ratio ≥ 0.9 respectively. 38 (34.9%) had total cholesterol ≥ 200 mg/dl, 43 (39.5%) had low density lipoprotein (LDL) cholesterol ≥ 130 mg/dl, 25 (22.9%) had triglycerides (TG) ≥ 150 mg/dl and 58 (53.2%) had High density lipoprotein (HDL) cholesterol < 40 mg/dl. Diabetes was significantly associated with factor levels below 5% (p = 0.038). BMI, waist circumference and dyslipidaemia in the study were significantly higher compared to the general population.

Conclusion: The study signifies an increased prevalence of risk factors for CVD among patients with haemophilia and the need for preventive measures.

Keywords: Cardiovascular disease, Haemophilia, Prevalence, Risk factors, Hypertension

Background
Haemophilia is a rare X linked recessive inherited bleeding disorder. [1]. Factor levels < 1%, 1–5% and > 5% are considered severe, moderate and mild respectively [2].

Over the past few decades, treatment of haemophilia has seen major advances thus the quality of life as well as the life expectancy of patients have increased [3–6]. With more patients living up to an older age, emergence of age-related comorbidities such as CVD in them have raised a concern [6]. As the treatment modalities for CVD are based on blood thinning and antiplatelet effects,
management of this group of patients has proved to be quite challenging due to their inherent bleeding tendency [7].

Hypertension, diabetes mellitus, dyslipidaemia, smoking and obesity are well known modifiable risk factors for CVD. Abdominal obesity in particular, is evidenced to exacerbate other risk factors and promote CVD [8]. Existing data suggest that the prevalence of these risk factors in patients with haemophilia is variable when compared with the general population [9–13].

Although traditionally it was believed that patients with haemophilia have a low risk for arterial thromboses due to their intrinsic hypocoagulable state, recent research data looking at the prevalence of CVD have shown mixed results [9, 11–13]. Several studies have demonstrated an increased risk of CVD and its risk factors in patients with haemophilia compared to the general population [9, 10].

In Sri Lanka, comprehensive care for patients with haemophilia has improved greatly over the years in keeping with the global trends. This study was performed with the aim of obtaining, prevalence data for CVD and risk factors among adult haemophilia patients since it is a timely need. Also, we aimed to compare the prevalence data with the existing data of the general population of the same gender, to find out whether there are any significant variations that might be resulting from the background coagulopathy.

Materials and methods
This descriptive cross-sectional study was carried out in the largest haemophilia center in Sri Lanka after obtaining ethical approval for the study from the Ethics Review Committee, Faculty of Medicine, University of Colombo, Sri Lanka (FERCAP accredited). All the patients ≥ 18 years of age attending the hemophilia clinic and consented were recruited to the study. Patients with uncertain factor levels and carrier women were excluded from the study. Socio-demographic data (age, race, religion, current employment and monthly family income), data on CVD events (coronary artery disease, non haemorrhagic stroke and transient ischaemic attack) and risk factors (diabetes, hypertension, dyslipidaemia and smoking status) were collected using a pre-tested, interviewer administered questionnaire and clinical records.

Height, waist and hip circumferences were measured to the nearest centimeter according to standard methods. Weight was measured into the nearest gram using standard methods [14, 15]. The BMI was calculated as the body weight in kilograms divided by the height in meters squared. The waist hip ratio was obtained by dividing waist circumference by hip circumference. After relaxing for 5–10 min, seated blood pressure (BP) was measured using a validated mercury sphygmomanometer using standard technique [16]. BP was measured twice with a gap of five minutes and averaged.

Venous blood samples were collected for fasting plasma glucose and lipid profile using standard techniques after an overnight fast of 12 h from the patients who were not diagnosed of having diabetes or dyslipidaemia respectively [17]. Samples were analyzed using a fully automated analyzer (Abbott architect c8000 biochemistry). The assay methods have been validated and appropriate quality control measures were applied to ensure reliability of results.

Participants were considered to have hypertension if they had been previously diagnosed (verified through previous medical records and anti-hypertensive prescriptions) or if the average of two resting seated BP readings, separated by 5 min were ≥ 140/90 mmHg [18]. Patients were considered to have diabetes if they had been previously diagnosed (verified through previous medical records, laboratory reports and prescriptions) or by having a fasting venous plasma glucose ≥ 126 mg/dl (World Health Organization and American Diabetes Association criteria) [19, 20]. Lipid profiles were categorized as normal and high according to National Cholesterol Education Programme/Adult Treatment Panel III (NCEP/ATP III) criteria [21].

The data were analyzed with SPSS 20 software. Prevalence of CVD and risk factors were determined by calculating the proportions and were compared with that of the general population. The significance of the differences between proportions (%) and means were tested using $\chi^2$-test and Student’s t-test, z test for proportions respectively. P values < 0.05 were considered significant.

Results
The total number of participants was 109 and the mean age of the study group was 37.7 ± 12.8 years. Majority (76.1%, n = 83) of the participants were employed and of 73.5% the monthly family income was > 10 000 LKR (50 USD) (Table 1).

Majority of the participants (84.4%, n = 92) had haemophilia A, and 51.4% (n = 56) had factor levels < 1%. Most of the participants (57.8%, n = 63) were on prophylaxis, while inhibitors had never been detected in 57.8% (n = 63) participants (Table 2).

The prevalence of at least one diagnosed CVD among the participants was 2.8% (n = 3) (Table 3).

Majority (53.2%) had HDL cholesterol < 40 mg/dl as a risk factor for CVD. The prevalence of risk factors in the study group is given in Table 4.

Prevalence of selected risk factors for CVD in the study group show significantly higher BMI, waist circumference and dyslipidaemia ($p < 0.00001$) compared to the age matched males (Table 5).
Of all the CVD risk factors, only diabetes was significantly associated with the severity of haemophilia (Table 6).

### Discussion

In this study, the prevalence of CVD and its risk factors in patients with haemophilia aged 18 and above in the largest treatment centre of Sri Lanka was assessed and compared with available data for the general population. Both haemophilia A and B patients were included in the study irrespective of their factor levels, inhibitor status or whether on prophylaxis. Majority of the participants (N = 94, 86.2%) in the study group were below 50 years of age. This reflects inclusion of younger patients in the prophylaxis program. In keeping with global statistics, majority (84%) of participants were having haemophilia A. Higher proportion (85.3%, n = 93) of the participants had either severe or moderate haemophilia.

Even though it is hypothesized that the severe form of haemophilia is protective against thrombotic events, existing literature has conflicting evidence on this [9–13]. Knowing prevalence of CVD and its risk factors among patients with haemophilia would enable implementing timely preventive measures.

In our study, there were three patients (2.8%) with coronary heart disease and one patient with non-haemorrhagic stroke. The participants with TIA and stroke also had coronary events in the past. Studies conducted to assess the prevalence of cardiovascular diseases in adult general population in Sri Lanka show prevalence of coronary heart disease in 16/1000 and prevalence of stroke and risk factors for stroke in 1/1000 although these are not directly comparable to the current study [24, 25].

Comparison of CVD risk factors of the study population with the data stated for males (n = 1758) in Sri Lanka diabetes and cardiovascular study (SLDCS) carried out in healthy participants who were aged ≥ 18 years shows that, dyslipidaemia, BMI and waist circumference were significantly higher among patients with haemophilia, than normal healthy adults [23]. According to SLDCS, prevalence of dyslipidaemia in Sri Lanka exceeds most of the regional and non-Asian countries. Further, it states that “Sri Lankans have a unique pattern of dyslipidaemia with lower HDL cholesterol, higher triglycerides and higher LDL cholesterol”. In our study, the prevalence of high LDL, TG and low HDL were 39.5%, 22.9% and 53.2% respectively, in keeping with the pattern described in the SLDCS.

In the retrospective study carried out by Ming Y. Lim et al. in 58 haemophilia patients attending the Mayo Comprehensive Haemophilia Clinic during 2006–2009 period, the prevalence of CVD risk factors was analyzed and compared with the existing data for the general population. They have found a higher prevalence of hypertension and a lower prevalence of current smoking and obesity. Diabetes in the sample was similar in prevalence to the general population statistics while they could not
assess the prevalence of dyslipidaemia due to missing data [26]. In a large US study (J. Pocoski et al. 2013), when compared to age-matched males in the general population, 2506 patients with haemophilia were found to have a significantly higher prevalence of coronary artery disease (10.7% vs 5.8%, P < 0.001), hypertension (22.6% vs 15.5%, P < 0.001) and hyperlipidaemia (15.9% vs 11.9%, P = 0.001). Also, they found that cardiovascular comorbidities in patients with haemophilia occurred at an earlier age than the general population. However, their study did not assess the prevalence of other CVD risk factors like obesity, diabetes, family history and smoking status and they have included only patients with haemophilia A. They have hypothesized that similar to other chronic inflammatory disorders, incidence of CVD might have increased in patients with haemophilia as they have chronically inflamed joints as a result of recurrent joint bleeds [10].

In a second retrospective database analysis, Pocoski J et al. were able to confirm the previous study findings of increased cardiovascular comorbidities in patients with haemophilia A in the US [27]. Significantly increased prevalence of obesity, increased waist circumference and dyslipidemia in the current study might have resulted from limited mobility and lack of proper physical exercise due to the fear of bleeding. Interestingly, the smoking habits were significantly lower in the study population compared to normal healthy adult males in Sri Lanka [23].

The significant association of diabetes mellitus observed in participants with severe haemophilia in the current study urge further studies to ascertain underlying causative factors. An increased prevalence of hypertension in patients with haemophilia was not evident in this study even though it was shown in several studies [10, 26, 28, 29].

### Table 3: Prevalence of cardiovascular diseases among the participants (N = 109)

| Disease                                      | Number of patients | %  |
|----------------------------------------------|--------------------|----|
| Angina                                       | 3                  | 2.8|
| Myocardial infarction                        | 3                  | 2.8|
| Undergone CABG or coronary stenting          | 3                  | 2.8|
| Transient ischemic attacks (TIA)             | 1                  | 0.9|
| Non hemorrhagic stroke                       | 1                  | 0.9|
| At least one CVD                             | 3                  | 2.8|

### Table 4: Prevalence of selected risk factors for cardiovascular diseases among the participants (N = 109)

| Risk factor                                      | Number of patients | %  |
|--------------------------------------------------|--------------------|----|
| Diabetes                                         | 10                 | 9.2|
| Hypertension                                     | 30                 | 27.5|
| Current smoking                                  | 13                 | 11.9|
| Obesity (BMI > 30 kg/m²) †                       | 4                  | 3.7|
| Overweight (BMI 25–29.9 kg/m²) †                 | 39                 | 35.8|
| Waist circumference ≥ 90 cm †                    | 32                 | 29.4|
| Waist hip ratio ≥ 0.9 †                          | 37                 | 33.9|
| Total cholesterol ≥ 200 mg/dl ‡                  | 38                 | 34.9|
| LDL cholesterol ≥ 130 mg/dl ‡                   | 43                 | 39.5|
| Triglycerides ≥ 150 mg/dl ‡                      | 25                 | 22.9|
| HDL cholesterol < 40 mg/dl ‡                    | 58                 | 53.2|

† World Health Organization defined cut off values[22]

‡ Categories according to National Cholesterol Education Programme/Adult Treatment Panel III guidelines[21]

### Table 5: Comparison of the prevalence of selected risk factors for cardiovascular diseases in the study with the general population

| Risk factor                                      | Study  | Sri Lanka diabetes and cardiovascular study [23] |
|--------------------------------------------------|--------|-------------------------------------------------|
| Diabetes (%)                                     | 9.2    | 11.3                                           |
| Hypertension (%)                                 | 27.5   | 27.1                                           |
| Current smoking (%)                              | 11.9   | 38.6                                           |
| BMI (kg/m²)                                      | 23.4 ± 3.8| 21.1 ± 3.7                                    |
| Waist circumference (cm)                         | 83.9 ± 11.1| 78.1 ± 11                                    |
| Dyslipidemia (%)                                 | 90.8   | 73.5                                           |

*p < 0.0001

### Table 6: Association between severity of haemophilia and risk factors for cardiovascular diseases

| Risk factor                                      | Factor level | P* |
|--------------------------------------------------|--------------|----|
| Diabetes                                         | < 5%         | N  | %   | 5–40% | N  | %   |
|                                                  |              |    |     |       |    |     |
| Diabetes                                         | 6            | 100.0| 400.0| 0.05  |
| Hypertension                                     | 25           | 83.3| 5    | 16.7  | 0.765|
| Obesity (BMI > 30 kg/m²)                         | 57           | 86.4| 9    | 13.6  | 0.126|
| Waist circumference ≥ 90 cm                      | 28           | 87.5| 4    | 12.5  | 0.774|
| Dyslipidemia                                     | 84           | 84.8| 15   | 15.2  | 1.000|

*p < 0.05

*p < 0.001
The main limitation in this study is the lack of a control group. In addition, although the prevalence of CVD in patients with haemophilia was calculated, it could not be compared with the healthy adult population of the country due to lack of a matched control group. Very low number of patients with actual CVD has made analysis of associations with factor levels and inhibitor status invalid. Also, there is a possibility of missing patients with actual CVD but no documentation, as we have considered only those with a clearly documented history of CVD as positive.

Conclusions and recommendations

The prevalence of diabetes mellitus, dyslipidaemia, increased BMI, waist circumference and cardiovascular events were substantially high among patients with haemophilia. This stresses the need for screening and active measures to control these risk factors to prevent cardiovascular events in patients with haemophilia. Further research using larger sample size and active control groups are recommended to validate these findings.

Abbreviations

BMI: Body mass index; BP: Blood pressure; CABG: Coronary Artery Bypass Grafting; CVD: Cardiovascular disease; HDL: High Density Lipoprotein; FERCAP: Forum for Ethical Review Committees in the Asian and Western Pacific Region; LDL: Low Density Lipoprotein; LKR: Sri Lankan Rupees; NCEP/ATP III: National Cholesterol Education Programme/Adult Treatment Panel III; NHSL: National Hospital of Sri Lanka; SLDCS: Sri Lanka diabetes and cardiovascular study; TG: Triglycerides; TIA: Transient Ischaemic Attack; USD: United States Dollar.

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Author contributions

TV, CW and VR designed the study. TV and GK collected data. CHR did the statistical analysis. TV, CW and CHR wrote the paper. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical clearance for this study was obtained by the Ethical Review Committee, Faculty of Medicine, University of Colombo, Sri Lanka (FERCAP accredited) (Ref. number – EC – 19 - 001) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed written consent was taken from all the volunteer participants of the study.

Consent for publication

Informed written consent for publication without direct personal identification details (such as name and address) was obtained from all the participants.

Competing interests

The authors have no competing interests.

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