

Gender: does it have a role in bleeding time in Caucasians with well controlled type 2 diabetes?

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Abstract

Background: Bleeding times are decreased in type 2 diabetics presenting an enhanced risk of myocardial infarction and subsequent death. It is controversial whether males have a greater risk of myocardial infarction and resultant death in type 2 diabetes. **Objective:** The purpose of this study was to review the literature regarding gender in bleeding time and to test the hypothesis that there would be gender inequality in bleeding time in well-controlled Caucasian Type 2 diabetics in Cape Breton, Nova Scotia. This study revealed significantly shorter bleeding times in males. Thus it may be that males should be more aggressively treated to increase bleeding time and hence to more equitably manage the risk of myocardial infarction and subsequent death. Ultimately it will have to be determined what bleeding time thresholds are suitable for intervention and indeed what the most appropriate intervention is at each threshold and what role gender may play in these features in type 2 diabetics. However, this was only a very small study and a much larger one would answer whether there is gender inequality in bleeding time among persons with well-controlled type 2 diabetes.

Keywords: *Bleeding time, diabetes, gender*

Introduction

Cape Breton Island in the province of Nova Scotia, Canada suffers from among the highest rates of type 2 diabetes in Canada, the consequences of which are seen in the overall economy and in the competition for healthcare dollars with other health issues. Consequently it is important to control this disease as much as possible so as to reduce its economic and social impact. There are no reports to date regarding the equity of management of bleeding time anywhere, such information being of clear importance for the medical, economic and social impacts of this disease.

Type 2 diabetes increases the risk of atherosclerosis-induced myocardial infarction and subsequent death.^{1,2,3} Myocardial infarction may result from the formation of thrombi and/or emboli in type 2 diabetics^{4,5} It was hypothesized that as the preponderance of studies show a greater risk of myocardial infarction and subsequent death in male type 2 diabetics,^{6,7,8,9} there should be a shorter bleeding time in males. However, other studies show a greater risk of myocardial infarction and subsequent death in female type 2 diabetics.^{10,11,12}

Bleeding time reflects platelet function and activation as well as interactions between endothelial cells in the artery,

platelet aggregation and the coagulation pathways.^{13,14,15}

Shortened bleeding time represents enhanced platelet reactivity and aggregation is related to myocardial infarction,^{16,17,18,19,20} though this view is not universally held.^{21,22,23} Nonetheless, risk of thrombosis is predicted by bleeding time.²⁴ Bleeding time is dramatically shorter in type 2 diabetics²⁵ with a corresponding increase in platelet aggregability.²⁶ In healthy individuals there is no gender difference in bleeding times according to Lethagen and Kling²⁷, though O'Brien²⁸ reports that males have a shorter bleeding time. However, no work has ever been done to assess potential gender difference in bleeding times in type 2 diabetics. The purpose of this work was to determine if there was a significant difference between bleeding times in male versus female Caucasian type 2 diabetics that are well controlled. Ultimately bleeding time thresholds for intervention will have to be established and what intervention is appropriate for each threshold on a gender basis.

Methods

Subjects (n =20 male, 20 female) were randomly chosen from among 84 Caucasians responding in approximately equal sex numbers to a Sydney, Nova Scotia newspaper advertisement and two area physicians. This study received approval from the Cape Breton University Human Ethics Review Committee. Subjects came for visit 1 and 3 months later for visit 2. On both visits, body weight and height were determined. Bleeding time was measured via the Ivy bleeding time²⁹ using the Simplate II R device and following the manufacturer's (Organon Teknika, Durham, North Carolina, USA) directions.

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Table 1: Pre-treatment characteristics of subjects (all Caucasian). Data (N = 32) is reported as mean \pm standard error of the mean (S.E.M.)

	Males visit 1	Males visit 2	Females visit 1	Females visit 2	Males –mean of visits 1 and 2	Females-mean of visits 1 and 2
N	18	18	14	14	18	14
Age (years)	59.5 \pm 1.7	60.7 \pm 2.9	60.7 \pm 2.9	60.7 \pm 2.9	59.5 \pm 1.7	60.7 \pm 2.9
Body mass index (BMI) kg/m ²	30.3 \pm 0.7	30.3 \pm 0.8	33.7 \pm 1.6	33.4 \pm 1.7	30.3 \pm 0.8	33.6 \pm 1.8

Table 2: Bleeding time in seconds, Data (N = 32) is reported as mean \pm standard error of the mean (S.E.M.). Statistically significant differences are marked with a superscript letters with different letters representing a statistically significant difference across a row.

	Males visit 1	Males visit 2	Females visit 1	Females visit 2	Males –mean of visits 1 and 2	Females-mean of visits 1 and 2
N	18	18	14	14	18	14
Bleeding time (seconds)	204.3 \pm 17.2	208.5 \pm 18.2	234.7 \pm 21.3	243.6 \pm 23.3	206.0 \pm 18.1	239.3 \pm 16.4 ^a

^a Significantly different from males (mean of visits one and two). There were no significant differences for a given gender between visits one and two. Males had significantly shorter bleeding time at visit one and at visit two.

Statistical analyses

The data in table 2 was analysed by an unpaired t-test for male versus female for each of visits 1, 2, and the combined visits 1 and 2. Bleeding times were done to determine to assess the possibility of gender differences in bleeding time (Table 2).

Results

Subject characteristics are contained in table 1. There were no significant differences in BMI between visits for males or females nor was there any difference between males and females in age or BMI for either visit 1 or 2. Bleeding times are found in table 2. Males had significantly shorter bleeding times compared to females (visit 1, visit 2, and visits 1 and 2 combined).

Discussion

The bleeding time data is validated by its consistency between visits one and two or for the two visits combined. The reason for the shorter bleeding time in males is not clear as medications, smoking, diet including alcohol consumption and exercise patterns were consistent between males and females for both visits one and two. Platelet function and activation^{13,14,15} as well as interactions between endothelial cells in the artery, platelets and the coagulation pathways^{16,17} are reflected in bleeding time. However, the higher platelet function, activation and interactions between arterial endothelial cells, platelets and coagulation pathways are consistent with the shorter bleeding times in healthy males compared to females.²⁸ No explanation has been established for the shorter bleeding times in healthy or type 2 diabetic males. The shorter bleeding times in males is consistent with the preponderance of studies listed above suggesting a greater risk of myocardial infarction in males compared to female type 2 diabetics suggesting that thrombi/emboli formation,

myocardial infarction risk and subsequent death are all related. Thus, it appears that males may be in greater need of intervention to increase bleeding times than females though both may require intervention to overcome this risk factor for myocardial infarction and potential subsequent death. However, not every type 2 diabetic is prescribed agents to reduce platelet aggregation. One review paper lends credence to the usefulness of bleeding time as a measure of platelet reactivity³⁰ while another review paper³¹ further emphasises the validity of the studies above.¹³⁻¹⁷ This shorter bleeding time is consistent with the findings of platelet hyperaggregation in type 2 diabetes in patients not taking insulin³² and gives support to anti-platelet agents used in some type 2 diabetes in patients managing the disease without insulin³³. That said, it remains to be established if the shorter bleeding time in type 2 diabetic males or if bleeding time at all is a useful indicator of myocardial infarction risk and subsequent death due to thrombi/emboli formation in any given person with type 2 diabetes. However, the current study was only a very small study and a much larger one would answer whether there is gender inequality in bleeding time among persons with well-controlled type 2 diabetes and whether bleeding time is a useful clinical indicator of whether males are in greater need of bleeding time prolongation agents. If bleeding time is such a useful indicator then ultimately bleeding time thresholds for intervention will have to be established and what intervention is appropriate for each threshold. The role of gender and dose in any in specific bleeding time intervention threshold also remains to be determined.

In conclusion, Caucasian type 2 diabetic males may require more aggressive intervention to increase bleeding times than do Caucasian type 2 diabetic females. However, both sexes have substantially shortened bleeding times and this would

appear to present a considerable risk of myocardial infarction and potential subsequent death.

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