Original Article **OPEN ACCESS**

Whole blood viscosity assessment issues V: Prevalence in hypercreatinaemia, hyperglycaemia and hyperlipidaemia

Ezekiel Uba Nwose

Western Pathology Cluster – NSW Health, South West Pathology Service; 590 Smollett Street Albury, Australia.

Citation: Nwose EU. Whole blood viscosity assessment issues V: Prevalence in hypercreatinaemia, hyperglycaemia and hyperlipidaemia. **North Am J Med Sci** 2010; 2: 403-408.
Doi: 10.4297/najms.2010.2408
Availability: www.najms.org
ISSN: 1947 – 2714

Abstract

Background: Diabetes and kidney failure are chronic diseases that are associated with cardiovascular complications, while dyslipidaemia is a strong risk factor. Hyperviscosity is believed to be associated and managed with antiplatelet, but not routinely assessed. **Aims**: This work investigates the prevalence of hyperviscosity in diabetes, dyslipidaemia and renal failure with a view to determine the proportion of patients who may not require antiplatelet therapy. **Materials and Methods**: Archived clinical pathology data for the period of 1999 to 2008 were utilized. 50,162-cases concomitantly tested for blood sugar, creatinine and lipid profile, as well as haematocrit and total proteins in five alternate years were extracted. The prevalence of different viscosity ranges associated with positive results was evaluated. **Results**: Hyperviscosity is about 4% prevalent in hyperglycemia and hyperlipidaemia, less in hypercreatinaemia. Hypoviscosity has statistically significantly the least <2.5% prevalent, while normoviscosity is most prevalent. Reverse analyses affirm that higher levels of hyperglycemia and hyperlipidaemia are statistically significant more associated with fourth compared to first quartile viscosity ($p < 0.01$). **Conclusion**: Previous report demonstrated that hypoviscosity is synonymous to high international normalized ratio where anticoagulant/antiplatelet is not recommended. This study demonstrates that up to 97.5% of cases investigated for chronic diseases could benefit from antiplatelet medication. This report corroborates with previous reports that hyperviscosity may not be very frequent. However, the level of stasis associated with laboratory evidence-based chronic disease affirms that the subclinical vasculopathy should be managed, and laboratory monitoring will provide clinical evidence base.

Keywords: Cardiovascular complications, chronic diseases, clinical laboratory evaluation, hypercreatinaemia, hyperglycemia, hyperlipidaemia, whole blood viscosity.

Correspondence to: Ezekiel Uba Nwose, Western Pathology Cluster – NSW Health, South West Pathology Service; 590 Smollett Street Albury, NSW 2640, Australia. Tel.: +612 60561651, Email: ezekiel.nwose@gsahs.health.nsw.gov.au

Introduction

As a clinical management strategy, patients with chronic disease such as diabetes, dyslipidaemia and renal failure require assessment of inflammation and subclinical cardiovascular complications. The laboratory indices include blood viscosity, which has been an established concept of three phenomena that ultimately lead to, and/or result from cardiovascular complications [1-3]. However, whole blood viscosity (WBV) is most often not performed even in the western world where there is capacity and facility to do so.

In diabetes, it is known that hyperviscosity is strongly influenced by the excellence of glycaemic control [4-6]. In a previous study, hyperglycaemic index (HBA1c) was used to identify the diabetes subjects who are undergoing management and monitoring. WBV levels in poorly controlled and excellently groups were compared using student's t-test. The results showed that WBV is statistically significantly lower in the group with excellent glycaemic control compared to the group with poor glycaemic control. This report provided further evidence that WBV is worse in poorly controlled diabetes as well as demonstrated that extrapolation of WBV level from haematocrit and plasma protein values is a feasible and valid method to employ in diabetes management [6]. However, the prevalence of abnormal blood viscosity in

diabetes has yet to be established.

In dyslipidaemia, cardiovascular disease is a complication [7]. One of the theories is that hypercholesterolemia contributes to atherosclerosis by increasing blood viscosity, which in turn complicates endothelial damage and thrombosis [8]. Further, oxidative stress is a factor in hypercholesterolaemia-induced atherogenesis whereby in tandem antioxidant defense protects against lipid peroxidation and atherosclerosis. For instance, there is evidence that severe hypercholesterolaemia may not be associated with development of atherosclerosis [9]. There is also report that though hypercholesterolaemia is associated with blood viscosity, the effect of lipid-lowering therapy is inconsistent on blood viscosity [7].

It has been depicted in patients with renal failure (RF) that oxidative stress is exacerbated during haemodialysis [10], as well as increase in WBV [11]. This underlies one of modes of cardiovascular disease complications in RF, and the essence of aspirin therapy. It is also reported that preoperative aspirin therapy, by its antiplatelet effect, offers protective effect against postoperative renal injury and improving renal perfusion possibly by reducing blood viscosity but not without bleeding complications [12]. All of these sum up to imply assessment of WBV in RF would benefit some patients. Further, hypoalbuminaemia associated with RF is a cause of hyperviscosity by enhancing a reduction in erythrocyte deformability [13]. There is the contrary belief in some quarters that anemia impacts low blood viscosity in people with RF, especially those at end stage [14]. There is also the implication of hypercreatinaemia being associated with anemia [15]. These could mean renal failure being associated with hypoviscosity. Therefore, there are contrasting possibilities WBV associations with RF, which require a study to enable formulation of an opinion whether high or low blood viscosity is more prevalent in RF.

Thus, it is unknown whether increased WBV vis-à-vis hyperviscosity is significantly prevalent in conditions where there is laboratory evidence of dyslipidaemia, hyperglycemia and/or renal failure. Further, whether such prevalence is significantly higher relative to where laboratory tests are negative would be worthy to establish. One of the interests of the series of "WBV issues" is to determine whether WBV is unduly highly sensitive and less specific. The hypothesis is that hyperviscosity would be highly prevalent in the sub-populations with higher levels of fasting blood sugar (FBS), hypercholesterolaemia (total cholesterol/high density lipoprotein ratio – i.e. TC/HDL ratio) and serum creatinine (S. Cr) compared to apparently normal sub-populations. This hypothesis is founded on the premise that diabetes, dyslipidaemia and renal failure are pathologies strongly complicating cardiovascular disease, which involve changes in blood viscosity levels as a subclinical vasculopathy. Diabetes, dyslipidaemia and renal failure are indicated FBS, TC/HDL ratio and S. Cr respectively.

The objective of this work is to investigate the prevalence of hyperviscosity in diabetes, dyslipidaemia and renal failure including (i) whether hyperviscosity is significantly more prevalent in sub-populations of FBS, TC/HDL ratio and S. Cr positive results compared to the prevalence in negative results; and (ii) whether FBS, TC/HDL ratio and S. Cr levels are higher more associated with hyperviscosity group compared to hypo-to-normoviscosity group. This study is premised on the hypothesis that hyperviscosity should be more prevalent than hypoviscosity in chronic diseases. The findings from this study will lend credence to whether WBV test result showing increased level should be considered a complication worth managing in the chronic diseases.

Materials and Methods

This work is part of Translational Biomedical Science Research initiative of the author. It is supported materially by the Albury South West Pathology – a unit of Western Pathology Cluster of NSW Health Australia. The Ethics Committee of the Area Health Service granted request through the Operations Manager for the use of de-identified data. Ten years de-identified archived clinical pathology data for the period of January 1999 to December 2008 constitutes the database. 50,162-cases tested for FBS, lipid profile and S. Cr from alternate years including 2000, 2002, 2004, 2006 and 2008 were extracted. Selection was limited to those that were concomitantly tested for all parameters as well as haematocrit and total proteins from the same phlebotomy collection time.

WBV at high shear stress was determined from haematocrit and total proteins as previously published [16]. Results of WBV were categorized within the continuum into levels of ≤15.00, 15.01-19.01 and ≥19.02 as indicative of low, normal and high WBV levels respectively. TC/HDL ratio was calculated from the lipid profile results. The ratio 5.0 was taken as cut off value. Any TC/HDL value >5.0 was considered dyslipidaemia/hypercholesterolaemia in this study. FBS results were categorized within the continuum into levels of ≤5.5, 5.6-7.0 and ≥7.1 as indicative of normoglycaemia, prediabetic and diabetic levels respectively. The reference range for prediabetes in this study was based on the recommendation contained in the guideline of the Diabetes Australia [17]. S. Cr level of 120μmol/L was taken as baseline for both genders in this study. A level ≥120μmol/L was considered to indicate renal disease.

First, all data were sorted in descending order by FBS, S. Cr and TC/HDL ratio. Following the protocol previously employed in this study series [18], the topmost (n = 120) with all positive biochemistry (co-pathologies +), and bottom (n = 120) with all negative biochemistry (co-pathologies -) sub-populations were selected. It was considered to avoid errors due to unequal sample size such as exaggerating the effects of inequality of variance [19, 20]. The discretional criterion for selection of (n = 120) representing each sub-population was to make the comparison be between the laboratory evidence-based

co-morbidity vs. apparently normal biochemistry. Comparison of actual WBV levels between sub-populations was performed by student's t-test.

Univariate data sets of FBS, S. Cr and TC/HDL ratio were sorted and separately sub-grouped into normo- and hyper-subpopulations. The prevalence of WBV categories in the subpopulations were evaluated by Two-Sample Kolmogorov-Smirnov Test.

In a reverse comparison, the levels of FBS, S Cr and TC/HDL ratio associated with the WBV groups were determined. Also following the same precaution against unequal sample size between groups as well as the protocol of comparing between highest-median-lowest WBV categories, (n = 935) in the low WBV group was used as baseline to select the topmost and median data size from the high and normal WBV groups respectively. Therefore, MANOVA was performed on a data subset (n = 2,805) comprising 935 in each group, using S-Plus version 6.1.

Results

Table 1 Summary of group statistics

Group		1	2	3
WBV (208 Sec-1)		≥ 19.02	15.01 - 19.01	≤15.00
N	Female	353	23,850	622
	Male	1,044	23,980	313
	Total	1,397	47,830	935
Age (Year)	Max	94	101	100
	Min	16	0.5*	18
	Mean	54	58	67
Fasting blood sugar (mmol/L)	Mean	5.9	5.7	5.6
	Median	5.4	5.3	5.1
	SD	2.0	1.7	1.8
	Max	33.3	34.2	19.9
	Min	1.0	0.4	0.4
S. Creatinine (µmol/L)	Mean	89	84	108
	Median	87	81	83
	SD	22	30	99
	Max	305	1,057	1,122
	Min	22	14	23
TC/HDL ratio	Mean	5.6	4.2	3.9
	Median	4.3	4.0	3.6
	SD	1.5	1.4	1.7
	Max	18.3	90.0	30.0
	Min	1.4	1.0	1.5

WBV: whole blood viscosity at high shear rate, N: number or sample size, TC: total cholesterol, HDL: high density lipoprotein; *Less than 1-year approximated.

Table 1 shows the summary demographics of data (Table 1). From the first analyses involving comparison of WBV levels in FBS, TC/HDL and S. Cr sub-populations, it is observed that the mean WBV level associated with the (all abnormal biochemistry) subpopulation is statistically significantly higher compared with the (all normal biochemistry) subpopulation (Fig 1, $p < 0.02$).

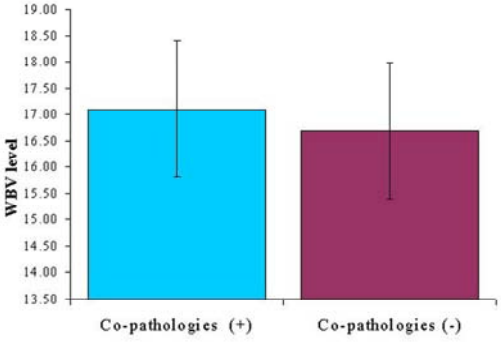

Fig. 1 Comparison of blood viscosity levels between negative and positive pathology. Co-pathologies: combination of fasting blood sugar, serum creatinine and TC/HDL ratio; WBV: whole blood viscosity; (-): normal biochemistry results; (+): positive biochemistry results.

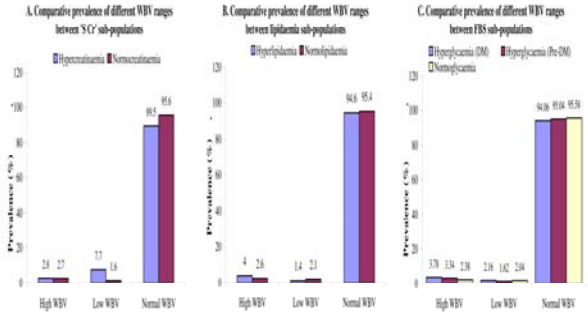

Fig. 2 Comparative prevalence of WBV categories in different biochemistry subpopulations. DM: diabetic, FBS: fasting blood sugar, Pre-DM: prediabetic; S. Cr: serum creatinine; WBV: whole blood viscosity.

Table 2 Prevalence of WBV categories subpopulations of hyper- and normocreatinaemia

	Cumulative hypercreatinaemia				Cumulative normocreatinaemia			
	N	WBV high (%)†	WBV low (%)	WBV normal (%)	N	WBV high (%)	WBV low (%)	WBV normal (%)
2000	204	3.0	5.4	91.6	3,851	3	1.8	95.2
2002	322	1.9	11.5	86.6	6,659	1.6	2.7	95.7
2004	585	2.3	5.4	92.3	8,864	2.6	1.1	96.3
2006	610	4.3	7.2	88.5	12,878	4.1	1.3	94.6
2008	700	2.5	9.1	88.4	15,489	2.4	1.3	96.3

†Average = 2.8%; WBV = whole blood viscosity

Table 3 Prevalence of WBV categories subpopulations of hyper- and normolipidaemia

	Cumulative hyperlipidaemia				Cumulative normolipidaemia			
	N	WBV high (%)†	WBV low (%)‡	WBV normal (%)	N	WBV high (%)	WBV low (%)‡	WBV normal (%)
2000	655	3.4	1.0	95.6	3,400	2.9	2.2	94.9
2002	1,211	2.0	2.8	95.2	5,770	1.5	3.2	95.3
2004	1,314	4.2	0.9	94.9	8,135	2.4	1.4	96.2
2006	2,132	6.0	1.2	92.8	11,356	3.8	1.7	94.5
2008	2,098	4.5	1.0	94.5	14,091	2.2	1.8	96

†Average = 4.0%; ‡average <2.5; WBV = whole blood viscosity

Table 4 Prevalence of WBV categories subpopulations of hyper- and normoglycaemia

	Hyperglycaemia (diabetic)				Hyperglycaemia (prediabetic)				Normoglycaemia			
	N	WBV-H (%)†	WBV-L (%)‡	WBV-N (%)	N	WBV-H (%)††	WBV-L (%)‡	WBV-N (%)	N	WBV-H (%)	WBV-L (%)‡	WBV-N (%)
2000	324	7.2	1.8	91.0	1,143	4.0	1.4	94.6	2,588	2.0	2.3	95.7
2002	717	2.0	3.3	94.7	2,130	2.1	2.7	95.2	4,134	1.4	3.3	95.3
2004	915	3.7	1.2	95.1	2,032	2.7	1.3	96	6,502	2.4	1.3	96.3
2006	1,215	3.5	2.3	94.2	3,349	5.2	1.1	93.7	8,924	3.8	1.7	94.5
2008	1,516	2.5	2.2	95.3	3,910	2.7	1.6	95.7	10,763	2.3	1.6	96.1

†Average = 3.8%; ††average = 3.3%; ‡average <2.5%; WBV = whole blood viscosity

Tables 2-4 show the cumulative prevalence of the different WBV categories associated with the subpopulations of hyper- and normo- creatinaemia, glycaemia and lipidaemia. Univariate analyses show that normal WBV is statistically significantly more prevalent in all sub-populations of hyper- and normo- creatinaemia, glycaemia and lipidaemia in comparison with high and/or low WBV (Tables 2 – 4).

Though hyperviscosity and hypoviscosity are of very low prevalence, the following observations are noted.

- The prevalence of high WBV is not different between hypercreatinaemia vs. normocreatinaemia. Low viscosity is significantly higher in hypercreatinaemia, while normal WBV is significantly higher in normocreatinaemia (Fig. 2a)
- The prevalence of high WBV is more in hyperlipidaemia compared to normolipidaemia sub-population (Fig. 2b).
- High WBV is also more prevalent in hyperglycaemia compared to normoglycaemia (Fig. 2c). This observation is consistent in all the years evaluated (Table 4)

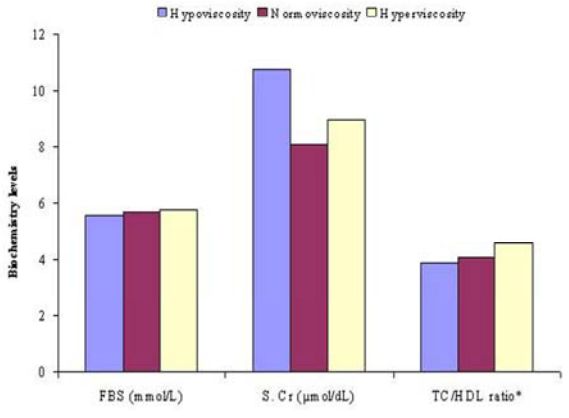

Fig. 3 Comparison of creatinaemia, glycaemia and lipidaemia between WBV groups. *averaged standard deviation for TC/HDL: 1.5, FBS: fasting blood sugar (averaged Standard deviation: 1.8), HDL: high density lipoprotein, S. Cr: serum creatinine (averaged standard deviation: 4.7, TC: total cholesterol, WBV: whole blood viscosity.

In comparison of absolute FBS, TC/HDL and S. Cr levels between the WBV groups, it is observed that biochemistry levels differ between categories (MANOVA=0). Univariate analyses further affirm the summary results presented in Table 1. That is, hyperviscosity is associated with the worst hyperglycaemia (P<0.01) and hyperlipidaemia (p=0). Conversely, hypoviscosity is associated with the lowest fasting blood glucose and cholesterol measures. Although lowest leve of S. Cr is associated with the normoviscosity group, no directional association between WBV and S. Cr levels were observed (Fig. 3).

Discussion

This issue of the series has sought to compare as well as establish the prevalence of hyperviscosity and hypoviscosity in chronic diseases using laboratory-based evidence. The results show a low prevalence of hyperviscosity among people who have laboratory evidence of possible chronic diseases, as indicated by FBS, S. Cr and/or TC/HDL ratio. However, the relatively low prevalence of hyperviscosity is statistically significantly greater when compared to the subpopulation that tested normal for any of the routine biochemistry markers. The cumulative prevalence of the different categories of WBV observed among subpopulations of hyper- and normal S. Cr (Table 2), as well as those of TC/HDL ratio (Table 3) and FBS (Table 4) affirm previous observations in this series that normal WBV level is consistently the most prevalent in general population.

There is probably no debate regarding normoviscosity being most prevalent in the general population. There is, however, a role for the measurement of other indices of subclinical vasculopathies vis-à-vis Virchow's triad that are implicated in chronic diseases. Blood viscosity is one option as an index of stasis, which has the capacity to lead to cardiovascular complications. The issue here is that WBV is not being assessed routinely in patients who have chronic diseases such as diabetes, dyslipidaemia or kidney disease.

Although, data from this study indicate average hyperglycaemia across all WBV groups, the results indicate that the opposite hyperviscosity vs. hypoviscosity are associated with the equally opposite highest vs. lowest fasting blood glucose and TC/HDL ratio measures respectively (Fig. 3). Though, the report does not support the hypothesis in part with regards to kidney disease, the observations support the hypothesis in part that high WBV is relatively more prevalent, and hence sensitive to the potential subclinical vasculopathy, in hyperglycaemia and dyslipidaemia. At this juncture, two

facts are imperative to note. First, many of the patients who have been assessed for these laboratory indices were apparently unhealthy and probably treated with drugs that include antiplatelet agents. The implication is that such medical therapies would have impacted reduction in WBV level, which in turn would have influenced observation of more prevalence of low WBV than high WBV. Second, the recommended reference values for WBV in this series are for conventional discussion. It was based on reference ranges of 37% – 54% haematocrit and 60 – 78g/L total proteins [16]. When the practice of every clinical pathology laboratory should develop its own reference values applicable to their particular population is employed, it would be expected prevalence will differ in favor of greater prevalence of high WBV. For instance, those laboratories employing 46% haematocrit as upper limit will observe much more than the 4% reported prevalence of hyperviscosity, while those laboratories considering haematocrit level of 32% as normal will observe a much lower prevalence of hypoviscosity. The import point of emphasis is that the prevalence of hyperviscosity in chronic diseases is significant enough to assess as part of evidence-based intervention against cardiovascular complications.

Surely, if <3% prevalence of prediabetes in overweight is worthy of note [21], it is thinkable that a possible >4% prevalence of vasculopathy associated with abnormal clinical biochemistry should require attention. It has been recognized that while a reduction in the incidence of venous stasis syndrome can impact on sudden death, effective and safe use of prophylaxis antiplatelet when risk is unavoidable, as well as targeting only those persons who will benefit most from the therapeutic dose is an important factor [22].

The previous issue in this series identified that low viscosity syndrome is synonymous with high international normalized ratio (INR), which is a contraindication for anticoagulant and/or antiplatelet therapy [23]. This issue identifies that low viscosity is <2.5% prevalent in people evaluated for dyslipidaemia and hyperglycaemia. While the vast majority who has normoviscosity would benefit from prophylactic dosage, those with hyperviscosity really have stasis requiring antiplatelet therapeutic dose.

WBV impacts on vessel wall adaptation to acute or chronic flow changes [14]. However, aspirin as a non steroidal anti-inflammatory drug is often withdrawn from renal disease patients, because it is believed to impact negatively on renal functions and exacerbate cardiovascular complications [24]. This study failed to observe consistent or unidirectional increase in WBV level associated with increasing serum creatinine. However, it highlights the need to assess WBV with a view to consider discrete and/or substitute antiplatelet therapy among individuals with kidney disease.

Conclusion

It has been demonstrated in earlier issue of this series that hypoviscosity is synonymous to high international normalized ratio where anticoagulant/antiplatelet is likely to be associated with bleeding side-effect. This report indicates that up to 97.5% of cases investigated for chronic diseases do not have hypoviscosity, and therefore could benefit from either prophylaxis or therapeutic medication depending on whether WBV is normal or high respectively. The issue addressed here is that laboratory monitoring of stasis using WBV measures could provide evidence base for antiplatelet in patients who are being investigated for hypercreatinaemia, hyperglycaemia or hyperlipidaemia.

Acknowledgement

Receipt of an approval from HREC committee of the Greater Southern Area Health Service, NSW Health was obtained, and hereby gratefully appreciated. The Operations Manager of the South West Pathology Service and Nathan Cann are appreciated for their contribution in data acquisition and collaboration in the research initiative. The Senior Scientists-in-Charge of biochemistry and haematology of the Albury South West Pathology Service are also appreciated for their support.

References

1. Mammen EF. Pathogenesis of venous thrombosis. Chest 1992; 102: 640S-644S.
2. Smith BD, La Celle PL. Blood viscosity and thrombosis: clinical considerations. Prog Hemost Thromb 1982; 6: 179-201.
3. Nwose EU, Jelinek HF, Richards RS, Kerr PG. Erythrocyte oxidative stress in clinical management of diabetes and its cardiovascular complication. Br J Biomed Sci 2007; 64: 35-43.
4. Caimi G, Presti RL. Techniques to evaluate erythrocyte deformability in diabetes mellitus. Acta Diabetol 2004; 41: 99-103.
5. Paisey RB, Harkness J, Hartog M, Chadwick T. The effect of improvement in diabetic control on plasma and whole blood viscosity. Diabetologia 1980; 19: 345-349.
6. Nwose EU, Butkowski E, Cann NG. Whole blood viscosity determination in diabetes management: perspective in practice. North Am J Med Sci 2009; 1: 110-113.
7. Ambrosi P, Juhan-Vague I. Dyslipidemia, lipid lowering drugs and thrombosis. Arch Mal Coeur Vaiss 1995; 88: 1641-1645.
8. Sloop GD. A critical analysis of the role of cholesterol in atherogenesis. Atherosclerosis 1999; 142: 265-268.
9. Wittenstein B, Klein M, Finckh B, Ullrich K, Kohlschutter A. Plasma antioxidants in pediatric patients with glycogen storage disease, diabetes mellitus, and hypercholesterolemia. Free Radic Biol Med 2002; 33: 103-110.
10. Pieniazek A, Brzeszczynska J, Kruszynska I, Gwozdzinski K. Investigation of albumin properties in patients with chronic renal failure. Free Radical Research 2009; 43: 1008-1018.
11. Vaisman S, Kensey K, Cho Y. Effect of

hemodialysis on whole blood viscosity. Int J Artif Organs 2009; 32: 329-335.
12. Gerrah R, Ehrlich S, Tshori S, Sahar G. Beneficial effect of aspirin on renal function in patients with renal insufficiency postcardiac surgery. J Cardiovasc Surg (Torino) 2004; 45: 545-550.
13. Joles JA, Willekes-Koolschijn N, Koomans HA. Hypoalbuminemia causes high blood viscosity by increasing red cell lysophosphatidylcholine. Kidney Int 1997; 52: 761-770.
14. Verbeke FH, Agharazii M, Boutouyrie P, Pannier B, Guerin AP, London GM. Local shear stress and brachial artery functions in end-stage renal disease. J Am Soc Nephrol 2007; 18: 621-628.
15. Denton CP, Lapadula G, Mouthon L, Muller-Ladner U. Renal complications and scleroderma renal crisis. Rheumatology (Oxford) 2009; 48: iii32-iii35.
16. Nwose EU. Whole blood viscosity assessment issues I: Extrapolation chart and reference values. North Am J Med Sci 2010; 2: 165-169.
17. Twigg SM, Kamp MC, Davis TM, Neylon EK, Flack JR, Society AD, et al. Prediabetes: a position statement from the Australian Diabetes Society and Australian Diabetes Educators Association. Med J Aust 2007; 186: 461-465.
18. Nwose EU. Whole blood viscosity assessment issues II: prevalence in endothelial dysfunction and hypercoagulation. North Am J Med Sci 2010; 2: 252-257.
19. Ludbrook J. Issues in biomedical statistics: comparing means under normal distribution theory. Aust N Z J Surg 1995; 65: 267-272.
20. Ludbrook J. Statistics in biomedical laboratory and clinical science: applications, issues and pitfalls. Med Princ Pract 2008; 17: 1-13.
21. Williams DE, Cadwell BL, Cheng YJ, Cowie CC, Gregg EW, Geiss LS, et al. Prevalence of impaired fasting glucose and its relationship with cardiovascular disease risk factors in US adolescents, 1999–2000. Pediatrics 2005; 116: 1122-1126.
22. Heit JA. Risk factors for venous thromboembolism. Clin Chest Med 2003; 24: 1-12.
23. Nwose EU, Cann NG, Butkowski E. Whole blood viscosity assessment issues III: Association with international normalized ratio and thrombocytopenia North Am J Med Sci 2010; 2: 301-305.
24. McGettigan P, Platona A, Henry DA. Renal and cardiovascular toxicity of non-steroidal anti-inflammatory drugs. Inflammopharmacology 2000; 8: 1-18.