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Full Length Research Paper

Plasma von Willebrand factor level and its associated parameters: Reference ranges in Nigeria

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Von Willebrand factor (VWF) is a complex multimeric, multifunctional glycoprotein. It plays a primary role in haemostasis by forming platelet plugs at sites of vascular injury. The biological breakdown of VWF is mediated by a metalloprotease, ADAMTS-13. Both proteins are important in normal coagulation. Deficiencies in gene and or protein of VWF are associated with von Willebrand disease and those of ADAMTS-13 are associated with thrombotic thrombocytopenic purpura. The plasma VWF varies with some non-genetic and genetic factors such as ABO phenotypes. We aimed at establishing a normal range for VWF: Ag, VWF: CB and ADAMTS-13 in adult Nigerian population. We investigated three hundred and sixty (360) plasmas. They comprised of one hundred and forty-eight (148) blood groups O, ninety-eight (98) group A, ninety-five (95) group B and nineteen (19) AB blood groups. Subjects were aged between 20 to 60 years and they all gave their consent in accordance with the declarations of Helsinki. We determined their full blood count, ABO blood grouping and VWF: Ag level, VWF: CBA and ADAMTS-13 activity. Data show mean \pm 2 SD of VWF: Ag levels for blood group A (1.359 ± 0.17 IU/ml); B (1.338 ± 0.22 IU/ml); AB (1.326 ± 0.44 IU/ml); O (1.233 ± 0.27 IU/ml); non-O (1.323 ± 0.22 IU/ml) and 1.286 ± 0.25 IU/ml in all blood groups. Blood group O showed significantly lower VWF: Ag level than those of non-O blood group with $P < 0.01$. The expression level of VWF: CB assay in the blood groups were; A (0.784 ± 0.21 IU/ml); B (0.788 ± 0.16 IU/ml); O (0.630 ± 0.31 IU/ml); non-O (0.788 ± 0.19) and 0.720 ± 0.26 in all blood groups. Blood group O was significantly lower when compared with non-O blood group ($p < 0.0001$). The mean ADAMTS-13 activities were as follows: A ($113.9 \pm 23.95\%$); B ($113.5 \pm 19.45\%$); O ($131.6 \pm 23.9\%$); non O ($113.7 \pm 21.79\%$) and $121.5 \pm 24.40\%$ in all blood groups. ADAMTS-13 activity was significantly higher in blood group O when compared with non-O ($p < 0.001$). VWF: Ag level were higher compared to Caucasian values.

Keywords: Von Willebrand disease, ABO, von Willebrand factor, von Willebrand factor collagen binding and ADAMTS-13.

INTRODUCTION

Von Willebrand factor (VWF) is a multimeric multifunctional glycoprotein present in plasma and produced constitutively in vascular endothelium, platelets and sub endothelial connective tissue. Its monomer is

encoded by VWF gene located on chromosome 12p13. It plays an important role in primary haemostasis (Ruggeri, 1999) and functions as a carrier protein for factor VIII, thereby protecting it from proteolytic degradation by

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activated protein C. It bridges the gap between adhered platelets in lesioned vascular wall with the sub endothelium. It also contributes in firm platelet aggregation by attaching itself to the platelet membrane receptor (GpIb and GpIIb/IIIa). ABO blood group substances have been demonstrated on the N-linked oligosaccharide chains of circulating VWF. The biological breakdown of VWF is mediated by a metalloprotease, A disintegrin-like and metalloprotease domain (reprolysin type) with thrombospondin type 1 motifs (ADAMTS-13) encoded by a gene located on chromosome 9q34. Both proteins play a crucial role in normal coagulation. Genetic and non-genetic factors determine plasma VWF levels. ABO blood group accounts for 30% of the 66% of the genetic factors (Orstavik, 1990). Deficiency and or dysfunction in VWF is associated with von Willebrand's disease (VWD), one of the most common inherited bleeding disorder, that affects up to 1% of the general population (Sadler et al., 2000; Sadler, 1994; Rodeghiero et al., 1987). Those of ADAMTS-13 are associated with thrombotic thrombocytopenic purpura (TTP). The von Willebrand collagen binding assay (VWF: CBA) assess the adhesive property of VWF and this corresponds to the physiological role of VWF.

In developing countries there is limited information on VWD (Srivastava and Rodeghiero, 2005), and diagnostic capabilities are nonexistent in hospitals in south east Nigeria. Plasma VWF vary relative to ABO blood group and race (Coppola et al., 2003; Miller et al., 2003; Sukhu et al., 2003; Haley et al., 2002; O'Donnell and Laffan, 2001; Miller et al., 2001; Nitu-Whalley et al., 2000; Shima et al., 1995; Caekebeke-Peerlinck et al., 1989). Also, ABO blood group influences the rate of proteolysis of VWF by ADAMTS-13 (Bowen, 2003) and show relationship between thrombotic and coronary risk factor (Schleef et al., 2005; Ray et al., 2004). Selection of the normal range for VWF plasma level at the lower end of the reference range based on the ABO group might influence the clinical diagnosis of VWD. (Bauduer and Ducout, 2004; Miller et al., 2003). At the upper end of the range, there is increased evidence of elevated thrombosis risk with high level of VWF (van der Meer et al., 2004; Felmeden et al., 2003). We evaluated the influence of ABO blood group on plasma VWF: Ag, VWF: CB, ADAMTS-13 and platelets in apparently healthy Nigerian adults and compared our results with earlier reports, thereby establishing a reference range in our population for use by clinicians in the locality.

MATERIALS AND METHODS

Study subjects

Three hundred and sixty subjects were enrolled in this study. They comprised of subject with blood group O: (65 females and 83 males); A (52 females and 46 males); B (44 females and 51 males) and AB blood (6 females and 13 males). All subjects were aged between 20 to 60 years and all gave their consent in accordance

with the declarations of Helsinki. The University of Nigeria Research Ethics Committee approved the study NHREC/05/01/2008B. 5 ml of blood was collected. 2 ml was transferred into an EDTA bottle at a concentration of 1.2 mg of anhydrous salt per ml of blood. Three ml of blood was added into 3.2% Trisodium citrate in 5% HEPES at a concentration of 9 parts of blood to 1 part of the anticoagulant. Only apparently healthy subjects were enrolled in the study.

Full blood count and blood grouping test

The full blood count was performed using an automated haematology analyzer BC 5300 (mindray, china). ABO blood group was determined using potent anti-A, anti-B and anti AB with adequate controls. The subjects serum were grouped using appropriate cells- known A, B and O cells with adequate controls. The results were read microscopically using premiere MRP-3000T (America).

Enzyme linked immunosorbent assay (ELISA) for VWF: Ag and CBA, ADAMTS-13 activity

Von Willebrand's factor antigen, VWF: CBA and ADAMTS-13 activity in plasma were measured using commercial ELISA kits from Technoclone Vienna, Austria. (Technozyme VWF: Ag ELISA (Lot no. RA32B00), VWF: CBAELISA (Lot no. RB4900) and ADAMTS-13 activity (Lot no. RU3AB00), according to the manufacturer's instructions.

Statistical analysis

This was performed using Graph-pad prism v.5.1. Reference ranges were calculated as ± 2 SD about the mean. One way analysis of variance (ANOVA) was used to compare the mean of the variables in the various ABO blood groups. Dunn's multiple comparison test was used to compare means across the various blood groups. Pearson product moment correlation coefficient was used to compare relationship between VWF: Ag and other variables.

RESULTS

Expression levels of VWF: Ag and CB, ADAMTS-13 and Platelets counts based on the tested ABO blood groups

We investigated 360 apparently healthy Nigerian subjects. The subjects were categorized according to their blood groups. The analysed blood groups were as follows: O (65 females and 83 males); A: (52 females and 46 males); B: (44 females and 51 males) and AB: (6 females and 13 males). The mean expression level of VWF: Ag in group A: 1.359 ± 0.17 IU/ml; B: 1.338 ± 0.22 IU/ml; AB: 1.326 ± 0.44 IU/ml; O: 1.233 ± 0.27 IU/ml; non-O: 1.323 ± 0.22 IU/ml and 1.286 ± 0.25 IU/ml in all blood groups Figure 1a. Blood group O showed a significantly lower VWF: Ag level than those of non-O blood group ($P < 0.01$).

The mean expression of VWF: CB assay were A: 0.784 ± 0.21 IU/ml; B: 0.788 ± 0.16 IU/ml; O: 0.630 ± 0.31 IU/ml; non-O: 0.788 ± 0.19 IU/ml and 0.720 ± 0.26 IU/ml

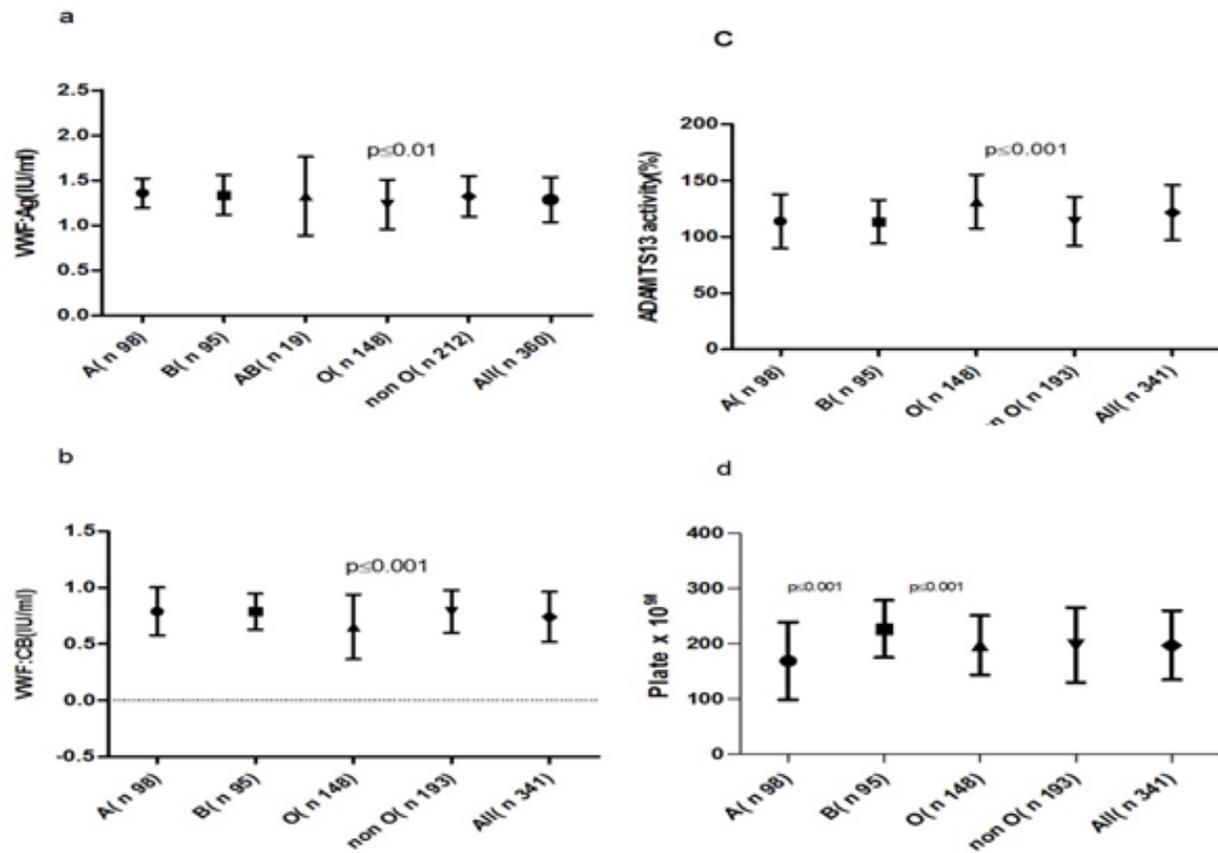


Figure 1. Plasma levels of VWF: Ag (a); VWF: CB(b); ADAMTS-13 (c) and platelet (d) in normal individuals with various ABO blood groups.

for all blood groups Figure 1b. Level of VWF: CB in blood group O was significantly lower when compared with non-O blood group $p < 0.0001$. ADAMTS-13 activities were as follows: A: $113.9 \pm 23.95\%$; B: $113.5 \pm 19.45\%$; O: $131.6 \pm 23.9\%$; non O: $113.7 \pm 21.79\%$ and $121.5 \pm 24.40\%$ for all blood groups Figure 1c. ADAMTS -13 activity was significantly higher in blood group O when compared with non- O $p < 0.001$. In addition, the mean platelet counts were as follows: A: $168.7 \pm 70.23 \times 10^9/L$; B: $226.7 \pm 51.96 \times 10^9/L$; O: $197.4 \pm 53.97 \times 10^9/L$; non-O: $197.5 \pm 68.7 \times 10^9/L$ and $197.3 \pm 62.38 \times 10^9/L$ in all blood groups Figure 1d. There was no significant difference between group O and non-O blood group. However, comparison between groups A and B showed a significant difference.

Relationships between levels of VWF: Ag and CB, ADAMTS -13 or Platelets

Figure 2 Presents the correlation (Pearson product moment correlation) coefficient (r) between VWF: Ag and VWF: CB, ADAMTS-13 or platelet in the various blood groups. Significant correlations were observed between platelet and VWF: Ag ($r = 0.1226$, $P = 0.02$); and

ADAMTS-13 with VWF: Ag ($r = 0.1202$ $P = 0.0205$) in all blood groups. In O blood group, VWF: CB and VWF: Ag showed significant correlation; $r = 0.3647$, $P = 0.001$. For non-O blood groups ADAMTS-13 and VWF: Ag correlated significantly $r = 0.8414$, $P = 0.0145$.

DISCUSSION

This is the first study addressing the effect of ABO blood group on VWF: Ag, VWF: CBA, platelets and ADAMTS-13 activity in Nigerian population. In this study, we investigate the plasma levels of VWF: Ag, VWF: CBA, ADAMTS-13 and platelet counts in the Igbo ethnic group of Nigeria the predominate tribe in the south east of Nigeria. We also examined the relationships of these variables between the ABO blood types and compared our results with previous data. Figure 3 shows the ABO related normal reference ranges identified from our study compared with data from previous studies. In these studies the VWF: Ag level increased in the various ABO groups in the following order: Erin et al. (2002), $O < All < non-O$, Masayuki et al. (1995) $OO < BO < AO < AA < AB < BB$, Gill et al. (1987) $O < A < B < AB$, Souto et al. (2000)

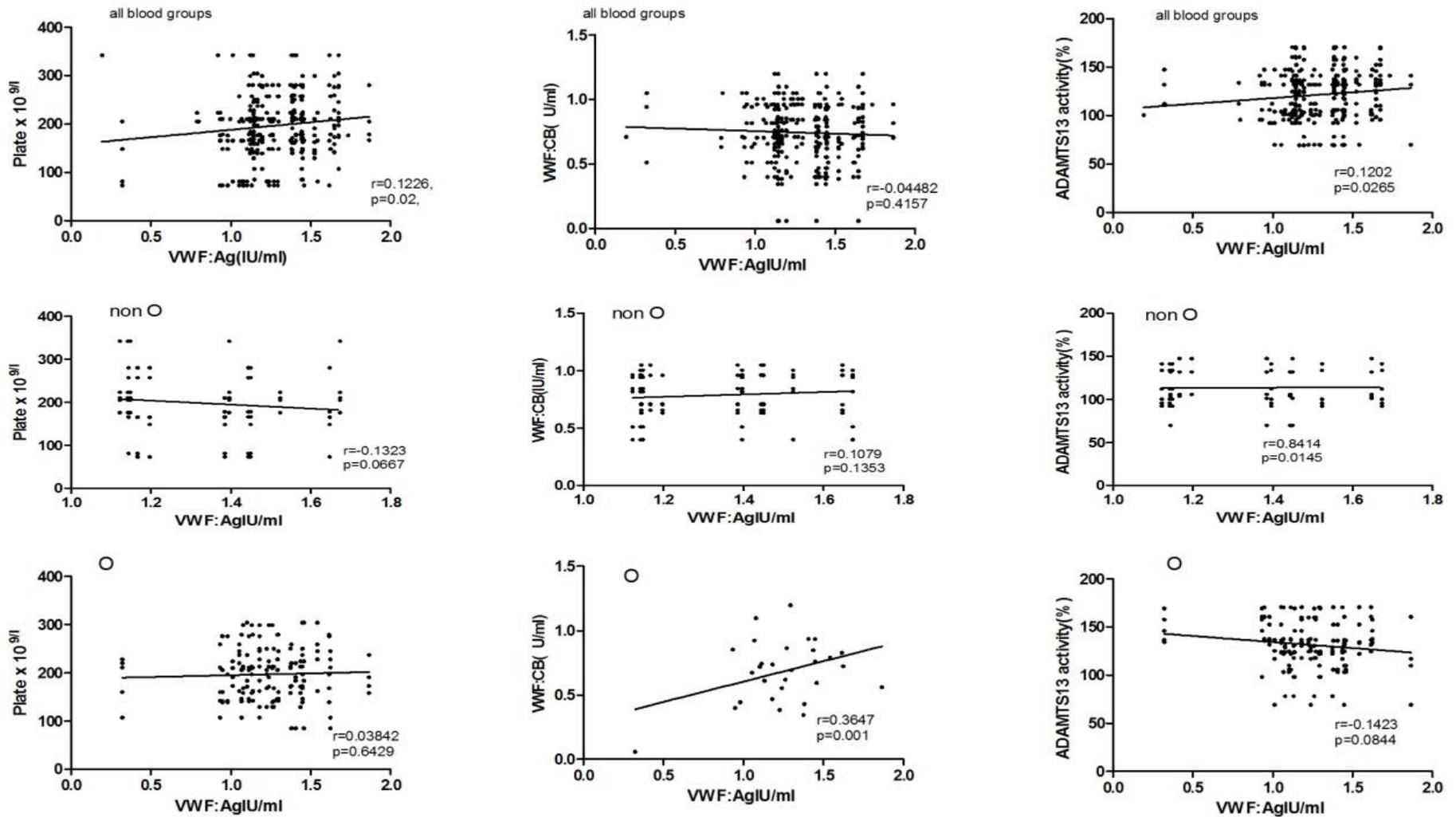


Figure 2. Relationship between VWF: Ag levels and platelet; WVF: CB or ADAMTS-13 in the plasma for the various blood groups.

O < BO < AO < AA < AB, Wee et al. (2005) O < All < non-O and this study O < AB < B < A. Group O plasmas showed the lowest level of VWF: Ag

in all the studies.

The sample number for our blood group AB may have contributed to the low level observed in this

study. Our result indicates that plasma VWF: Ag level increased in the following other O < AB < B < A. Group O subjects have significantly lower

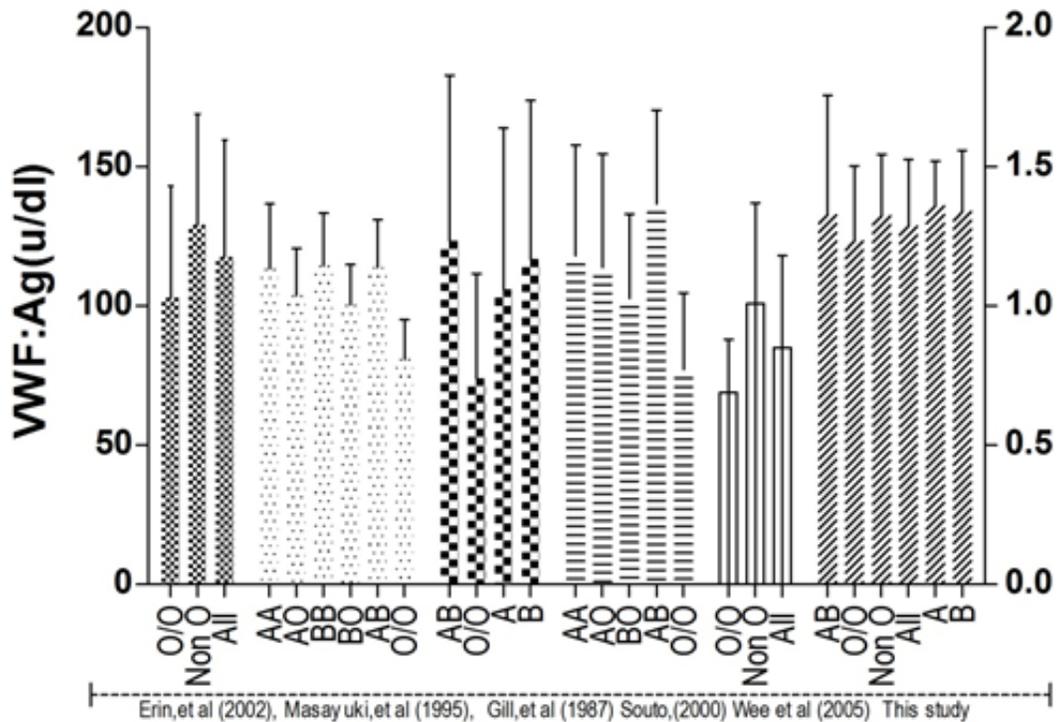


Figure 3. Reference ranges for VWF: Ag in various ABO blood groups identified in this study compared with previously published data.

plasma VWF: Ag levels than non-O individuals. This is consistent with earlier reports. Blood group O possesses the greatest amount of H substance and expression of H gene is inversely correlated to VWF: Ag level (O'Donnell et al., 2002). The actual ranges quoted by earlier reports varied greatly, this may be attributed to the genotype of the ABO blood group and other factors outside the VWF gene. The ranges determined in this study were higher when compared with Caucasian values determined by Miller et al. (2003). This may be explained because VWF is an acute phase reactant in man and our population is exposed to many conditions including malaria infestation that can predispose to an inflammatory response.

The VWF: CBA assess the adhesive property of VWF. The ability of VWF to bind collagen functions as a variable, which corresponds to the physiological role of VWF. VWF: CB was significantly lower in blood group O when compared with non-O blood. This is consistent with the observation in the Chinese population (Chng et al., 2005), Australia (Favaloro et al., 2005) and Atlanta (Miller et al., 2003). In this study, we also demonstrated a significant correlation between VWF: Ag and VWF: CB in blood group O subjects. The normal ratio of VWF: CB/VWF: Ag ranges from 1.59 to 1.99 in this study. ADAMTS-13 activity was significantly higher in blood group O subjects when compared with non-O blood group. This agrees with earlier reports (O'Donnell et al., 2005; Bowen, 2003). The activity of ADAMTS-13

increased as follows $B < A < O$ for this study. ADAMTS-13 activity in plasma has also been shown to be inversely related to plasma VWF: Ag level (Mannucci et al., 2004).

There was a significant correlation between VWF: Ag and platelet when all the groups were compared. Both variables increased or decreased together. An inverse relationship although not statistically significant is worth noting in non-O blood group. An inverse relationship between high platelet count and large VWF multimers in plasma have been reported (Ulrich et al., 1993). Platelet count of the adult Nigerian is lower than those of the Caucasians (Ukaejiofo et al., 1979) was also confirmed by this study. Gene expression studies will therefore further elucidate the relationship between VWF: Ag and platelets. A negative relationship was observed between ADAMTS-13 and VWF: Ag in blood group O subjects. This demonstrates the increased activity of ADAMTS-13 and reduced VWF: Ag level in blood group O. In other blood groups, this variable either increased or decreased together.

Large multimers of VWF are haemostatically active and are cleaved by ADAMTS-13. This function if defective may lead to various forms of thrombotic disorders. Conditions which may regulate the cleavage of VWF by ADAMTS-13 include-flow shear stress (Tsai, 1996; Tsai and Lian 1998; Tsai 2003), heparin sulphate, platelet glycoprotein-Iba (GP Iba) (Nishio et al., 2004), sodium chloride (De Cristofaro et al., 2005), inflammatory

cytokines (Bernardo et al., 2004) and haemoglobin (Studd et al., 2005). The mechanisms underlying the activity of ADAMTS-13 in the various blood groups need further investigations.

CONCLUSION

The ABO blood groups significantly affect VWF: Ag level, VWF: CBA, ADAMTS-13 activity and platelet counts in this study. Our reference ranges for VWF: Ag level were higher than results obtained from previous reports. This fact is to be considered while interpreting results for our population.

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Conflicts of interest

Authors have none to declare.

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