Homeostatic Model Assessment of Insulin Activity and Iron Profile among Regular Blood Donors at a Tertiary Health Centre, South-West Nigeria

Abstract

Context: Iron overload has been established to play a role in the etiopathogenesis of Type 2 diabetes mellitus (DM) as evidenced by its high prevalence among patients with hemochromatosis and transfusion-dependent diseases. This is as a result of iron redox reaction which generates free radicals that cause peroxidation of lipid-rich pancreas, leading to reduced insulin sensitivity. Aims: This study therefore evaluated the impact of regular blood donation, an effective method of reducing iron load, on β-islet cell functions and level of glycemic control among regular whole blood donors. Settings and Design: This is a cross-sectional, analytical study. Subjects and Methods: Forty-two consenting regular blood donors who had donated whole blood at least twice and not more than thrice in the last 1 year were selected as cases, while 42 age-matched individuals who have never donated blood previously were selected as controls. Samples were obtained and analyzed for fasting plasma glucose, fasting plasma insulin, serum ferritin, transferrin receptor, total iron-binding capacity (TIBC), and serum iron, while Homeostatic Model Assessment (HOMA) of insulin resistance (IR) and beta sensitivity, HOMA-IR, and HOMA-β-cell function (HOMA-β%) were calculated for both groups. Statistical Analysis Used: Statistical analysis was done using Microsoft Excel package and the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Results: Iron studies among regular blood donors and nondonors revealed lower serum iron (37.2 ± 7.3 vs. 41.1 ± 7.9 µmol/L, P = 0.180) and lower serum ferritin levels (30.2 ± 26.1 vs. 42.9 ± 38.5 ng/mL, P = 0.117), which were not statistically significant, while there were higher serum transferrin receptor (155.5 ± 22.6 vs. 112.8 ± 43.4 ng/mL, P < 0.001) and higher serum TIBC (42.3 ± 6.4 vs. 37.8 ± 7.4 µmol/L, P < 0.05), among cases than controls. The mean HOMA-IR and HOMA-β% were also significantly better among donors than nondonors. Conclusions: Regular blood donation may protect the body from the toxic effects of excessive iron store, which includes improved insulin sensitivity and glycemic control.

Keywords: Blood donation, ferritin, glucose, insulin, transferrin receptor

Introduction

Type 2 diabetes mellitus (DM) is a common manifestation of hemochromatosis, a disease of massive iron overload,[1] which has led to speculation that high iron stores may increase the risk of developing Type 2 DM irrespective of the etiology, acquired or congenital. High serum ferritin (mostly an indication of excess iron store), associated with Type 2 DM, has not been recognized as an entity in the current clinical guidelines for the management of Type 2 DM.[2] However, a cross-sectional, population study showed that mildly elevated serum ferritin was associated with elevated fasting serum insulin.[3] Nearly 53%–80% of patients with hemochromatosis develop DM, and there is a direct relationship between the concentration of the excess iron and development of DM in hemochromatosis.[4] Furthermore, there are evidences that fasting concentrations of serum insulin and blood glucose had raised in men with high serum concentrations of ferritin.[5] Patients with DM have also been found to have a higher mean serum ferritin concentrations than that in the general population.[5]

DM is one of the most common noncommunicable diseases, with rapidly increasing prevalence almost equaling that of infectious diseases in our environment. The nature of our diet and cooking utensils and the high incidences of infectious and noninfectious diseases requiring blood transfusion, including malaria, HIV/AIDS, and sickle cell disease, predispose us to iron overload, on β-islet cell functions and level of glycemic control among regular whole blood donors. This study evaluated the impact of regular blood donation, an effective method of reducing iron load, on β-islet cell functions and level of glycemic control among regular whole blood donors. This study therefore evaluated the impact of regular blood donation, an effective method of reducing iron load, on β-islet cell functions and level of glycemic control among regular whole blood donors. This study therefore evaluated the impact of regular blood donation, an effective method of reducing iron load, on β-islet cell functions and level of glycemic control among regular whole blood donors.

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overload, which has been linked to the etiopathogenesis of Type 2 DM. Because it is generally accepted that prevention is better than cure, this study will assess the impact of regular blood donation, a proven process of reducing excessive body iron store, on glycemic control among regular blood donors at our center.

Homeostatic Model Assessment (HOMA) is a method for assessing β-cell function and insulin resistance (IR) from basal (fasting) glucose and insulin or C-peptide concentrations. HOMA model is derived from a mathematical assessment of the interaction between β-cell function (HOMA-β%) and IR in an idealized model that is then used to compute steady-state insulin and glucose concentrations. HOMA1-IR = (FPI × FPG)/22.5 and HOMA1-β% = (20 × FPI)/(FPG − 3.5) for IR and β-cell function, respectively, where FPI is fasting plasma insulin concentration (mU/L) and FPG is fasting plasma glucose (mmol/L).[5]

This study aims to evaluate the impact of regular blood donation on glycemic control at the Federal Medical Centre, Abeokuta. This evaluation was carried out through assays of fasting plasma glucose (FPG), Fasting plasma insulin (FPI) and the parameters were used to estimate HOMA-IR and HOMA1-β% among subjects and controls While serum ferritin, serum transferrin receptors, serum iron and total iron binding capacity were assayed as markers of iron load.

Subjects and Methods

Ethical approval for this study was obtained from the Ethical Research Committee with protocol number FMCA/470/HREC/01/2019/04 of the Federal Medical Centre, Abeokuta. The study was conducted at the Department of Pathology, Federal Medical Centre, Abeokuta, Southwestern Nigeria. The hospital receives referrals of patients from Ogun State and other neighboring states. The hospital has a functional hematology unit under which there is a blood bank, for screening, processing, and storage of the donated blood.

The study population included 42 individuals who have donated blood at least twice or at most thrice in the last 1 year with a minimum of 12 weeks’ interval between each blood donation, while 42 individuals who have not donated blood in the last 1 year served as controls. It was a cross-sectional, analytical study of consecutive regular blood donors. Sampling was conducted using the convenient recruitment method. Individuals with ages between 18 and 40 years, males or females, and who have donated blood at least twice but not more than thrice in the last 1 year were selected as cases.

The minimum sample size required for the study was estimated using the Fisher formula,[7] which gave a sample size of 44.7. The sample size was rounded up to 42 cases and 42 controls. Exclusion criteria were known diabetic patients, patients on routine hematins and other iron-containing drugs, and patients with evidence of ongoing infections.

Five milliliters of blood samples was collected from the patients in plain vacutainer tubes and 5 ml in a fluoride oxalate vacutainer tube. The samples were allowed to clot and then centrifuged for 20 min at 3000 revolutions per min. Serum samples were separated and analyzed for insulin, ferritin, TIBC, and transferrin receptor, while plasma samples were analyzed for FPG. Analysis of FPG was done using Fortress Diagnostics’ glucose (LOT number 172663, Fortress Diagnostic limited, United Kingdom, glucose reagent), serum ferritin was assayed using Calbiotech insulin ELISA kit (LOT number INS5471), serum ferritin was assayed using Calbiotech ELISA kit (LOT number FR5621, Calbiotech ELISA Kits, CA, USA), TIBC and serum iron were assayed using Fortress diagnostic kit (LOT number 181400), and serum transferrin receptor 1 was assayed using Elabscience ELISA kit (LOT number 6XH1JSJQR, Elabscience Biotechnology Inc. USA ELISA kit).

Statistical analysis was done using Microsoft Excel package and the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as mean ± standard deviation. Parameters displaying P < 0.05 were considered statistically significant.

Table 1: Mean serum insulin, ferritin, transferrin receptor, total iron-binding capacity, serum iron, Homeostatic Model Assessment-Insulin Resistance and Homeostatic Model Assessment-β% among regular blood donors and nondonors

| Variable                      | Cases         | Controls       | t    | P      |
|-------------------------------|---------------|----------------|------|--------|
| Insulin (µIU/mL), mean±SD     | 9.0-12.0, 10.3±0.8 | 8.4-14.2, 10.7±1.5 | −1.420 | 0.164  |
| Ferritin (ng/mL), mean±SD     | 5.0-148.0, 30.2±26.1 | 5.0-137.0, 42.9±38.5 | −1.602 | 0.117  |
| Transferrin (ng/mL), mean±SD  | 74.0-182.0, 155.5±22.6 | 10.0-176.0, 112.8±43.4 | 6.372  | <0.001*|
| Glucose (mmol/L), mean±SD     | 4.0-6.0, 5.2±0.6 | 4.0-8.9, 6.6±2.2 | −3.937 | <0.001*|
| Iron (µmol/L), mean±SD        | 23.0-53.0, 37.2±7.3 | 20.0-58.0, 41.1±7.9 | −2.477 | 0.018  |
| TIBC (µmol/L), mean±SD        | 31.0-68.0, 42.3±6.4 | 27.0-56.0, 37.8±7.4 | 2.805  | 0.008* |
| HOMA-IR, mean±SD              | 1.0-3.0, 2.4±0.4 | 2.0-7.0, 3.2±1.2 | −4.048 | <0.001*|
| HOMA-β%, mean±SD              | 78.4-296.5, 141.4±72.8 | 21.6-213.2, 97.9±53.4 | 3.269  | 0.002* |

*P<0.05; SD: Standard deviation; t: Paired r-test; TIBC: Total iron-binding capacity; HOMA IR: Homeostatic Model Assessment-insulin resistance; SD: Standard deviation; HOMA-β%: Homeostatic Model Assessment of β-cell function
Results

A total of 84 male research participants, comprising 42 cases who donated blood at least twice and at most thrice in a year and 42 controls who did not donate blood at all in the last 1 year, involved in this research. The mean age of the cases was 31 ± 7.9 years and that of controls was 28 ± 6.9 years.

The mean serum iron was lower among cases than controls (37.2 ± 7.3 vs. 41.1 ± 7.9 µmol/L, \( P > 0.05 \)), and the comparison of mean was however not statistically significant. The mean serum ferritin was lower among cases than among the controls (30.2 ± 26.1 vs. 42.9 ± 38.5 ng/mL, \( P = 0.117 \)), and the comparison of mean was also not statistically significant. The mean serum transferrin was higher among cases than controls (155.5 ± 22.6 vs. 112.8 ± 43.4 ng/mL, \( P < 0.001 \)), and the comparison of mean was statistically significant [Figure 1 and Table 1].

The mean FPG among cases was lower than that among controls (5.2 ± 0.6 vs. 6.6 ± 2.2 mmol/L, \( P < 0.001 \)), and the difference was statistically significant. The mean fasting serum insulin among the cases was lower than that among controls (10.3 ± 0.8 vs. 10.7 ± 1.5 µIU/mL, \( P > 0.05 \)), and the difference was however not statistically significant. The mean HOMA-IR among the cases was lower than that among controls (2.4 ± 0.4 vs. 3.2 ± 1.2, \( P < 0.001 \)), and the difference was statistically significant. The mean HOMA-\( \beta \)% for the cases was higher than that among controls (141.4 ± 72.8 vs. 97.9 ± 53.4%, \( P > 0.05 \)), and the difference was however statistically not significant [Figure 2].

Discussion

The analysis of iron studies carried out among participants showed lower mean serum iron and lower mean serum ferritin levels among regular blood donors than nondonors, though the differences were not significant statistically. However, the mean serum transferrin receptors and TIBC were significantly higher among regular donors than nondonors. These showed that the iron store among donors was lower than that among nondonors though not the extent of being iron deficient. This is consistent with the findings in previous studies.\(^8,9\) Blood donation is, therefore, an efficient means of ridding the body’s excess iron stores and limits exposure to its toxic effects. One of the toxic effects of excess iron load is the generation of free radicals/reactive oxygen species (ROS), which causes peroxidation of lipid-rich organs including pancreas. This may over time lead to increased IR or reduced insulin sensitivity, manifesting clinically as impaired glucose tolerance or DM.\(^10\)

The mean serum fasting insulin and mean serum FPG in this study were lower among regular donors than that
among controls. This showed a better glycemic control among blood donors than nondonors. HOMA-IR, an objective assessment of the degree of IR, is lower among regular donors compared to nondonors, showing lower IR among donors than nondonors. In addition, regular donors showed higher insulin sensitivity than nondonors, with significantly higher HOMA-β% compared to nondonors. Excess iron is associated with increased risk of developing DM, and this relationship is thought to be causal so much so that excess iron even within serum reference interval has been found to have detrimental effects on insulin secretion, insulin sensitivity, adipokine levels, and metabolic flexibility.[11] Conditions associated with repeated transfusions such as thalassemia and sickle cell anemia have the potential of leading to the development of iron overload, and consequent insulin-dependent DM.[12]

Iron is a redox-active transitional metal that can catalyze the formation of hydroxyl ROS, which are highly potent oxidizing agents and have been implicated in the etiology of DM. This property, despite its important metabolic functions, makes iron potentially hazardous because of its ability to participate in the generation of powerful oxidant species such as hydroxyl radical.[13] This reaction is commonly referred to as the metal catalyzed Haber–Weiss reaction.[13]

The role of iron in the pathogenesis of diabetes is suggested by (1) an increased incidence of Type 2 DM in diverse causes of iron overload and (2) reversal or improvement in diabetes (glycemic control) with a reduction in iron load achieved using phlebotomy, blood donation, or utilization of iron chelation therapy. Recently, a link has been established between increased dietary iron intake, particularly eating red meat and increased body iron stores, increased serum ferritin, and the development of DM. This association is related to the high haem content of meat and increased dietary haem intake.[14] The exact mechanism of iron overload-induced diabetes is not fully cleared yet, and the suggested mechanism includes: (1) insulin deficiency, (2) IR, and (3) hepatic dysfunction.[10]

Le et al. suggested that serum ferritin concentration could be used as a biopredictor of DM.[15] This is similar to the findings in a meta-analysis which has showed that elevated levels of serum ferritin may help to identify individuals at risk of Type 2 DM.[16]

Conclusions

Regular blood donation is an effective means of ridding the body’s excessive iron store without necessarily becoming iron deficient, improving insulin sensitivity, ensuring good glycemic control, and protecting the body from the toxic effects of iron store.

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Conflicts of interest

There are no conflicts of interest.

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