# Original Article

# Serum copper and zinc levels in Nigerian type 2 diabetic patients

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## Abstract
Diabetes is characterised by high metabolic and oxidative stress, and there is evidence that trace elements such as zinc and copper are important co-factors in these processes. We therefore have measured serum zinc and copper levels in type 2 diabetic subjects from Nigeria. Fifty-three (53) diabetic patients and 50 age-matched non-diabetic control subjects were included in this study. Serum zinc, serum copper, and fasting plasma glucose (FPG) were measured among the diabetic and control groups and the association of both trace elements compared with glycaemic status, age, gender, and duration of diabetes. The serum zinc level was significantly lower (11.9±2.9 µmol/L) in diabetic patients as compared with control subjects (14.6±2.5 mmol/L, p<0.001). A significantly higher difference was observed in serum copper levels with a mean of 23.3±4.3 µmol/L in diabetic patients as compared with 19.9±3.9 µmol/L (p<0.001) in controls. There was no association with age, gender, glycaemic status, and duration of diabetes with the serum concentration of these trace elements in the type-2 diabetic patients studied.

## Introduction
Diabetes mellitus is a disorder of carbohydrate metabolism, leading to both metabolic and oxidative stress.[1] Type 2 diabetes is due to insulin resistance and/or insulin secretory defects, and accounts for almost 90% of all diabetic cases.[2]

Direct associations of trace and macro elements with diabetes have been observed in many research studies.[3] The proposed mechanism of trace elements enhancing insulin action includes activation of insulin receptor sites and serving as co-factors or components for enzyme systems involved in glucose metabolism.[4,5]

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Zinc serves as an essential co-factor for more than 200 enzymes, many of which regulate the metabolism of carbohydrates, lipids, and proteins. Insulin itself is believed to be stored in an inactive form of zinc crystals.[6] Zinc ions in the secretory granules of cells are known to glue insulin β molecules, creating somatically stable hexamers. When the secretory granules open to the surface, the zinc ions pressure decreases rapidly and pH levels change from acid to physiological levels, which results in free insulin monomers and zinc ions will be released from the pancreas.[7] Thus zinc is required for insulin synthesis and storage.[8] There is accumulating evidence that the metabolism of zinc is altered in type 1 diabetes and that zinc might have specific roles in the pathogenesis and progress of this disease.[9]

Copper is the third most abundant essential trace element in the body. Copper is present in the body combined with enzymes to form metalloenzymes such as caeruloplasmin and superoxide dismutase (SOD).[10] These enzymes play major roles in redox reactions, and antioxidant defence.[11] It has been postulated that copper possesses insulin–like activity and promotes lipogenesis.[12] Human studies demonstrate that diabetic patients may have abnormal levels of serum copper.[13]

The objective of this study was to determine the serum levels of zinc and copper in type 2 diabetic patients in our locality and their association with age, gender, glycaemic status, and duration of diabetes.

## Materials and methods
### Subjects
One hundred and three (103) people were recruited into this cross-sectional case control study over a 6-month period. Subjects were selected by a non-probability convenient sampling method, after obtaining well-informed written consent in accordance with the Helsinki declaration of 1975 on human experimentation.

Fifty-three (53) type-2 diabetic patients who had attended a secondary health facility in Osun State, Nigeria, for at least a year were recruited for this study. These patients were of both genders between the ages of 40 and 70 years. Fifty (50) age- and sex-matched non-diabetic control subjects were selected among the hospital staff and blood donors.

Exclusion criteria for both groups included in this study were: obesity, pregnancy, renal disease, hypertension, and finally those taking nutritional supplements, laxatives, diuretics, or alcohol.

## Sampling

After an overnight fast, blood samples were collected, at a standardised time to minimise any effect of diurnal variation, via venepuncture aseptically into fluoride oxalate tubes for fasting plasma glucose (FPG), and plain tubes (Vacutainer, Becton Dickson, Meylan, France) for serum copper and zinc determination. FPG was estimated using the glucose-oxidase method, while serum zinc and copper were analysed by graphite furnace atomic absorption spectrometry.

## Statistics

The SPSS 15.0 statistical package was used for data processing. Results obtained were summarized as mean (± standard deviation). Differences between the groups were compared using paired Student t-test, and the level of significance was set at $p<0.05$.

## Results

Out of 53 diabetic patients selected, 19 (36%) were males (mean age of 60±8 years) and 34 (64%) were female (mean age of 57±10 years. Fifty (50) age- and sex-matched healthy controls included 22 males (44%) with a mean age of 57±5 years, and 28 (56%) females with a mean age of 55±5 years. The mean FBG was 4.4 ± 0.7 mmol/L in conrols and 7.0 ± 0.5 mmol/L in the diabetic patients ($p<0.001$).

Mean serum zinc was significantly lower in diabetic patients compared with healthy subjects (11.9±2.9 vs 14.6±2.5 µmol/L, $p<0.001$), while serum copper levels were significantly higher compared with health subjects (23.3±4.3 vs 19.9±3.9 µmol/L, $p<0.001$). These results are summarised in Table 1).

*Table 1  Characteristics of the study subjects*

| Characteristics of the study subjects (n=103) | | | |
|---|---|---|---|
| **Parameter** | **Patient (n=53)** | **Control (n=50)** | **p value** |
| **Age (years)** | 58±9.3 | 56±5 | 0.2 |
| **Gender** Male Female | 19 (36%) 34 (64%) | 22 (44%) 28 (56%) | |
| **Duration of diabetes** ≤5 years >5 years | 43 (81%) 10 (19%) | Nil Nil | |
| **Trace elements** Zinc (µmol/L) Copper (µmol/L) FPG (mmol/L) | 12±3 23±4 7.0±0.46 | 15±3 20±4 4.4±0.72 | <0.001* <0.001* <0.001* |
| **Notes** Results are expressed as mean ± standard deviation FPG = Fasting plasma glucose * p value is statistically significant | | | |

The difference of serum zinc and copper in either gender was not statistically significant in the study group (p=0.9) or in the control group (p=0.6). Age was categorised into two groups (<50 years and >50 years) and had no statistically significant association with serum zinc, levels being higher both in the younger study group (p=0.7) and the younger controls (p=0.3). Likewise, serum copper was also found to show no statistically significant association in both categories of age in the study group (p=0.7) and in the control group (p=0.6).

Neither serum zinc nor serum copper showed any association with fasting blood sugar or with duration of diabetes.

## Discussion

Diabetes pathogenesis is considered multi-factorial, and the physiological role of copper and zinc has been implicated in the development and progress of the disease.[14] The serum levels of zinc and copper in type 2 diabetes and control groups were determined in this study and related to the age, gender, glycaemic status and duration of diabetes. It was observed that the mean serum zinc level was significantly lower in diabetics as compared to control subjects, an observation also reported by Anetor et al[15] and Al-Maroof and Al-Sharbatti.[16] The possible explanation of the observed hypozincemia in diabetes is hyperzincuria which occurs as a result of hyperglycaemia, disrupting the proper metabolism of trace elements. Despite the decrease in the zinc levels in diabetes in our study group there was no correlation between this trace element and their glucose levels.

The study also revealed that copper levels are increased in type 2 diabetes. The increased levels of copper in the diabetic patients compared with normal human subjects agrees with earlier reports[14,17]. The increase in the copper levels in patients with type 2 diabetes might be attributed to hyperglycemia, stimulating glycation, which results in the formation of highly reactive oxidants that can lead to tissue damage.[18,19]

## Conclusion

Further studies need to be carried out to determine the molecular role of copper and zinc in the development of diabetic complications in a larger Nigerian population. Also, glycated haemoglobin ($HbA_{1c}$) would be useful to measure in such studies (financial constraints prevented its use in the current study).

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# Original Article

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# Letter to the Editor

Dear AJDM Editor,

**Unregulated complementary and alternative medicine use among diabetic patients in Africa: A call for action**

In diabetes mellitus management, oral glucose-lowering drugs and insulin are the conventional modalities, along with crucial lifestyle change. Medications are however prohibitively expensive to many patients in Africa – for example, in Malawi where insulin can cost more than half a monthly salary.[1] These treatments are also associated with some adverse effects.[2] As a result, many patients opt for complementary and alternative medicine (CAM).

Despite the medical community posing concerns on CAM use, it is widely gaining popularity, in Africa and worldwide.[3,4] The frequency of CAM use is estimated at 80% in Africa, with other countries not far behind (52–70% in Australia, 40% in China, 49% in France, and 42% in the USA).[5] Of most concern are the many patients who mix CAM use with conventional medications or replace them completely, often without consultation with their doctor.[6]

Commonly used CAM therapies in diabetes include herbal medicines, nutritional supplements, spiritual healing, and relaxation techniques. Whilst some are harmless and may even assist mainstream therapies, many pose real health dangers.

This is not just about protecting the role of doctors or a pharmaceutical turf war. CAM use has been associated with fatalities and side-effects. Many contain one or more active ingredients with a range of biological and pharmacotherapeutic actions.[7] These actions are often inconsistent and improperly communicated to the consumer. Adverse effects may include: ketoacidosis due to insulin substitution and interactions with conventional drugs.[3,5]

Importantly, many CAM therapies have limited or variable efficacy, or have been reported to cause hypoglycaemia, as a result of inconsistent quality or dosing.[5] CAM use is also unregulated in most developing countries – with unregulated dosing and suppliers with little or no medical training. Moreover, limited quality assurance and regulatory processes exist, with CAM falling outside the scope of most government drug and therapeutic agencies in Africa, including Kenya.

So while patients have the right to use CAM, as always, the collective and individual's benefits must be weighed against the risks; and many concerns regarding CAM use are truly justified. Hence, legislation to govern CAM use is necessary and inevitable. These therapies should be subject to the same strict regulation and testing as all drugs.

The World Health Organization acknowledges CAM use, and even encourages member states to integrate CAM into national healthcare systems, but with caution and quality-checks.[5] China is one of the countries with such an integrated system,[7] but this integration is a challenge to many developing countries, including Kenya.

Finally, healthcare providers should routinely enquire whether patients use CAM and actively engage in discussions around their risks and benefits. Providers should also educate patients on the importance of taking their prescribed medication and avoiding CAM, which may interfere with their diabetes medications or cause side-effects. Therefore, there is need for a multi-sectoral action to regulate and streamline CAM use for diabetes patients in Africa.

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