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Effects of Long-Term Use of Zinc and Vitamin C on Type 2 Diabetes Mellitus and Its Complications

Maryam K. Aruoah

Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq

Abstract: The present study aims to use zinc and vitamin C supplements to treat diabetes mellitus disease and its complications, including diabetic foot ulcer, retinopathy, nephropathy, and neuropathy. Diabetes mellitus (DM) is recognized as the most common endocrine disease worldwide. A progressive and aggressive disease, it is characterized by both hyperglycemia and dyslipidemia. Diabetic foot ulcer is a well-known complication of the disease, and it is the most common reason for lower limb amputation. Retinopathy is another diabetic complication, which leads to blindness. Moreover, diabetic nephropathy is the main cause of chronic kidney disease. Zinc is an antioxidant element and a cofactor for more than 300 important enzymes. It is also involved in many important physiological metabolic functions. Vitamin C is a water-soluble vitamin and a powerful dietary antioxidant. It is also essential for the physiological functioning of the body. Zinc and vitamin C are closely related to DM and its complications. Fifty diabetic patients were selected to receive 100 mg zinc oxide tablets and 1000 mg vitamin C tablets every day for six months. The doses were separated and given at specified times during the day. Thirty healthy individuals comprised the control group. Wound swab cultures and antibiotic sensitivity tests were performed for the diabetic foot ulcer patients prior to the supplements being taken. A significant decrease was observed in the patients' fasting blood glucose, glycated hemoglobin, insulin hormone, urea, creatinine levels, blood pressure, and urination, while an improvement was seen in their lipid profile. Complete healing of the foot ulcers was achieved with blood flow signs and sensation and without the use of antibiotics in most cases. Clear improvements in visual acuity were also achieved. Indeed, type 2 DM is a metabolic disease that results from zinc deficiency, impairing insulin hormone production, secretion, and function. This causes an increase in fasting blood sugar, glycated hemoglobin, blood pressure, urination, and dyslipidemia. It also leads to the inability of vitamin C to enter the cells, followed by endothelial dysfunction, impaired blood flow, and ischemia, thereby leading to diabetic complications.

Keywords: type 2 diabetes mellitus, zinc, vitamin C, long-term complications, foot ulcer, retinopathy, nephropathy.

长期服用锌和维生素C对2型糖尿病及其并发症的影响

摘要:

本研究旨在使用锌和维生素C补充剂治疗糖尿病及其并发症，包括糖尿病足溃疡、视网膜病变、肾病和神经病变。糖尿病（DM）被公认为全球最常见的内分泌疾病。它是一种进行性和侵袭性的疾病，以高血糖和血脂异常为特征。糖尿病足溃疡是一种众所周知的并发症，也是下肢截肢的最常见原因。视网膜病变是另一种导致失明的糖尿病并发症。此外，糖尿病肾病是慢性肾病的主要原因。锌是一种抗氧化元素，也是300多种重要酶的辅助因子。它还参与许多重要的生理代谢功能。维生素C是一种水溶性维生素，是一种强大的膳食抗氧化剂。它对身体的生理功能也很重要。锌和维生素C与DM及其并发症密切相关。选择50名糖尿病患者，每天服用100毫克氧化锌片和1000毫克维生素C片，持续6个月。在一天中的特定时间分开给药。三十名健康人组成对照组。在服用补充剂之前，对糖尿病足溃疡患者进行伤口拭子培养和抗生素敏感性测试。观察到患者的空腹血糖、糖化血红蛋白、胰岛素激素、尿素、肌酐

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About the author: Maryam K. Aruoah, Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq
Corresponding author Maryam K. Aruoah, MaryamBio2112@gmail.com

水平、血压和排尿显着下降，而血脂水平则有所改善。在大多数情况下，足部溃疡完全愈合，有血流迹象和感觉，无需使用抗生素。还实现了视力的明显改善。事实上，2型DM是一种由锌缺乏引起的代谢疾病，会损害胰岛素激素的产生、分泌和功能。这会导致空腹血糖、糖化血红蛋白、血压、排尿和血脂异常升高。它还导致维生素C无法进入细胞，继而导致内皮功能障碍、血流受损和缺血，从而导致糖尿病并发症。

关键词：2型糖尿病、锌、维生素C、长期并发症、足溃疡、视网膜病变、肾病。

Abbreviations

DM – diabetes mellitus; T1DM – type 1 diabetes mellitus; T2DM – type 2 diabetes mellitus; IDDM – insulin-dependent diabetes mellitus; NIDDM – non-insulin-dependent diabetes mellitus; Zn – zinc; VC – vitamin C; NO – nitric oxide; eNOS – endothelial nitric oxide synthase; HbA1C – glycated hemoglobin; HDL – high-density lipoprotein; LDL – low-density lipoprotein; VLDL – very-low-density lipoprotein; FBG – fasting blood glucose; TC – total cholesterol; TG – triglycerides; CV – cardiovascular.

1. Introduction

Diabetes mellitus (DM) is the most common endocrine disease worldwide. It is characterized by hyperglycemia, which causes an increase in the blood glucose concentration (fasting blood glucose ≥ 126 mg/dL) [1, 2]. Chronic hyperglycemia, which is common in cases of DM, results from the disruption of carbohydrate, protein, and fat metabolism. Thus, hyperglycemia is associated not only with an imbalance in carbohydrate metabolism, but also with an imbalance in lipid and protein metabolism. An increase in the blood glucose concentration is generally due to insufficient or inefficient insulin production within the body [3, 4].

There are three types of DM, namely type 1 DM, type 2 DM, and gestational DM. Type 2 DM (T2DM) is recognized as the most common type worldwide, accounting for approximately 85%–95% of all DM cases [2, 3]. It is also known as non-insulin-dependent DM (NIDDM). As a consequence of T2DM, the cells' response to insulin fails [5]. Thus, T2DM is characterized by hyperinsulinemia and insulin resistance, which can range from predominant insulin resistance with proportional insulin deficiency to a dominant secretion defect associated with β-cell dysfunction and failure [6, 7].

T1DM and T2DM share the same symptoms, namely excessive urination, increased thirst, increased hunger, unexplained weight loss, slow healing of wounds and skin infections, feet numbness, wasting of the muscles, fatigue, cramps, constipation, and blurry vision [5, 8]. However, the symptoms of T1DM develop more quickly, typically within days or weeks.

Zinc (Zn) is recognized as a vital nutrient in relation to human health [9]. In addition, it is essential for the growth and development of animals, plants, and microorganisms. More specifically, Zn has acute effects on homeostasis. Significant public health problems and concerns are related to Zn deficiency [10]. Zn-dependent enzymes exist within all known enzyme classes [9]. Moreover, Zn plays important structural, regulatory, and catalytical biological roles within the body [9]. It also plays an important role in physiological metabolism [11]. Rich dietary sources of Zn include shellfish, beef, and other red meats, while nuts and legumes are comparatively good plant sources. Other good sources of Zn include mushrooms, edible fungi, daylily flowers, black sesame, cabbage, dates, hazelnuts, black rice, other vegetables, and fruits [9].

Vitamin C (VC) is a water-soluble vitamin and a powerful dietary antioxidant. It is also a generous donor of electrons, which means that it aids in the scavenging mechanism [12]. It is essential and vital for the body's normal physiological functions [13]. VC (also known as ascorbate or ascorbic acid) is a simple low-molecular-weight carbohydrate [14]. The main dietary sources of VC are citrus fruits, tomatoes, and green chilies. Dairy products represent minor sources of VC [12].

Endothelial dysfunction involves a decrease in the bioavailability of nitric oxide (NO), which is derived by means of the action of endothelial nitric oxide synthase (eNOS) [15]. T2DM is known to be related to endothelial dysfunction. Both disorders can develop into micro- and macrovascular complications, which represent the main causes of morbidity and mortality worldwide [2].

In fact, vascular complications are vital to the destructive effects of DM and occur due to hyperglycemia, which indicates a link between DM and oxidative stress [16]. Generally, as mentioned above, such complications can be categorized into macro- and microvascular complications [16]. Smeltzer and Bare defined macrovascular complications as atherosclerotic changes in the larger blood vessels. Moreover, the main macrovascular complications associated with DM are:

1. Cardiovascular diseases (most commonly coronary artery disease);

2. Cerebral vascular diseases;
3. Peripheral vascular diseases [16].

By contrast, microvascular complications are defined as damage to the small blood vessels, which generally develops in cases of DM. The likelihood of microvascular lesions occurring is influenced by the thickness of the basement membrane of the capillaries and arterioles of the blood vessels found in the retina and kidney. The major microvascular complications and their results are:

1. Retinopathy leads to blindness;
2. Nephropathy leads to end-stage renal disease;
3. Neuropathy leads to various painful neuropathies [16].

HbA1C is, indirectly, a measure of average blood glucose levels [17]. The diagnosis of diabetes is based on the threshold of HbA1C for the development of microvascular disease. It is a better predictor for cardiovascular CV events than fasting blood glucose (FBG) or two-hour postprandial glucose (2hPPG) [7].

Hypertension, defined as constant high blood pressure (140/90 mmHg), is common among diabetic patients. Hypertension is the main risk factor for microvascular complications [17].

Insulin is the principal glucose regulatory hormone. Primarily, insulin increases facilitated glucose transport into the cells, thus reducing blood glucose levels [12]. It is produced by beta (β) cells of the endocrine pancreas within specialized areas called the islets of Langerhans [18]. Accordingly, the secretion of insulin hormone is strictly controlled by:

1. Glucose;
2. Hormones;
3. Autonomic nervous system activities [19].

Urea is formed when amino acids are exposed to oxidative deamination in which ammonia is produced and moved to the liver to create urea through the urea cycle. Uremia is a state in which a raised blood urea level affects kidney function [20]. Creatinine serum level is one of the indicators for examining renal function, and it is the most common measurement of kidney function [20, 21].

Diabetic dyslipidemia features a triad of elevated triglycerides, decreased high-density lipoprotein (HDL), and extra small, concentrated, low-density lipoprotein (LDL) particles. These abnormalities in lipid profile are predominant in diabetes mellitus due to insulin resistance or deficiency and impact key enzymes and the pathways in lipid metabolism. It has been suggested that the conformation of lipid particles in diabetic dyslipidemia is more atherogenic compared with other kinds of dyslipidemia [22, 23].

A diabetic foot ulcer is one of the complications of diabetes mellitus and causes worldwide high-cost morbidity [24]. The diabetic foot comprises an infection, ulceration, and destruction of the deep tissues related to neurological abnormalities and peripheral vascular diseases in the lower limbs [25]. Foot infections are the most common complications of diabetic foot ulcers and play the main role in moist gangrene development [26]. Diabetic foot ulcers eventually lead to gangrene development; if not treated adequately, they may lead to amputation and death [26]. Diabetic patients have a 15-fold higher risk of amputating lower limbs, and every 20 seconds a lower limb is lost to a diabetic patient somewhere in the world [27].

The exact mechanism underlying diabetic ulceration is not well known yet, although several mechanisms have been suggested comprising genetic factors. However, peripheral neuropathy constitutes the main cause of arterial insufficiency [28].

2. Materials and Methods

This study was conducted according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human patients were approved by the ethics committees of the University of Baghdad on October 9, 2018 (Number 3006) and the Kirkuk Health Department on October 15, 2018 (Number 29877). Verbal informed consent was obtained from all patients.

2.1. Subjects

There were 80 subjects in total, namely:

- 50 diabetic patients: 30 diabetic patients without foot ulcers (10 men and 20 women; 30-65 years old); and 20 diabetic patients with foot ulcers (13 men and 7 women; 30-65 years old).
- 30 healthy persons as a control group (16 men and 14 women; 30- 65 years old).

All patients attended either Azadi Teaching Hospital or Kirkuk General Hospital in Kirkuk city, Iraq. Their body mass index (BMI) ranged from 22- 24.7 kg/m^2, and the duration of their disease was from 5 to 25 years.

2.1.1. Diagnosis

Patients were previously diagnosed with diabetes mellitus by the hospitals mentioned above.

2.1.2. Exclusion

Patients with obesity or drinking alcohol were excluded.

2.1.3. Doses and Administration Times

Patients received 100mg zinc oxide tablets and 1000 mg vitamin C tablets every day for 6 months. The doses were separated and were given at specified times during the day. The details about doses and times are below.

2.1.4. Type of Samples

Whole blood, serum, and wound pus.

2.1.5. Analysis and Others

FBG, HbA1C, serum insulin hormone, lipids profile, serum creatinine, blood urea, serum zinc, and serum vitamin C levels were analyzed in the laboratory. Blood pressure was determined using a Sphygmomanometer, visual acuity by Snellen Eye Chart, and urination times by asking the patient. The parameters were measured for all groups before the supplements taking; while, after the supplements taking, they were measured for the patients' groups only. Wound swab cultures and antibiotic sensitivity tests were done for patients with diabetic foot ulcers before taking supplements only.

2.2. Statistical Analysis

The data were analyzed using SAS 2012. Statistical Analysis System, User's Guide. Statistical. Version 9.1th ed. SAS. Inst. Inc. Cary. N.C. USA, by using Statistical Package for the Social Sciences (SPPS) program.

2.3. Doses of Zinc Element and Vitamin C Supplements

2.3.1. Zinc Dose

Zinc was administrated at a dose of 100 mg. This dose is considered higher than the daily dose. The recommended daily nutritional requirement of zinc is estimated at 15 mg/day [10]. However, the 100mg dose in our study was specified according to many considerations related to following physiological aspects of diabetes:

1. Urination times are higher in diabetic patients than in healthy persons. Hypozincaemia and hyperzincuria are well-known in patients with both type-1 and type-2 diabetes mellitus [29]. Zinc levels in serum are reduced in Type 1 and Type 2 diabetes mellitus because of zinc loss due to excessive urination [5, 10]. Also, several research studies have shown that hyperglycemia interferes with the active transport of zinc back into the renal tubular cells, which leads to hyperzincuria and thus, it is more excreted in diabetes mellitus state [11].
2. Zinc is a water-soluble element, and it is not stored effectively in body tissues [9].
3. Diabetes has been described by several research studies as a pro-inflammatory state, leading to oxidative stress resulting in increased free radicals and decreased antioxidant weaponry [13, 19, 30]. The antioxidant characteristics of zinc also make it be consumed more in diabetes mellitus state [29].
4. Zinc ions are hydrophilic and do not cross cell membranes by passive diffusion. Transport has been described as having both saturable and non-saturable mechanisms, depending on the zinc concentrations present [10]. For this reason, its concentration must be higher than required.

2.3.2. Vitamin C Dose

Vitamin C was administrated at a 1000 mg dose.

There were many causes behind this higher dose:

1. Increased requirements and decreased vitamin C intake in the body [31].
2. Diabetes is described by a pro-inflammatory state, which leads to oxidative stress that produces free radicals [13, 19]. Vitamin C is a powerful dietary antioxidant [12]. So it is more consumed in the diabetes mellitus state.
3. Most animals can synthesize vitamin C from (glucose-6-phosphate), and their endogenous synthesis rises during stress. However, humans have lost the capability to synthesize vitamin C because of mutations in L-gulono-g-lactonoxidase that encodes the terminal stage of vitamin C synthesis [31]. So the body is dependent on exogenous sources completely.
4. Dietary intake is sufficient to preserve vitamin C levels within the normal range during normal conditions. However, increased requests may lead to insufficiency [31].
5. Vitamin C is found in the lymphocytes abundantly. Therefore its levels decrease during inflammation and infection [12].
6. Both glucose and vitamin C require help from insulin before they can penetrate the cell membranes using special pumps. High glucose levels obstruct vitamin C entry into the cell. During hyperglycemia, the uptake of vitamin C into cells is impaired [12]. So it cannot enter the cell. Vitamin C (VC) is a water-soluble vitamin [12]. Hence, it is excreted in the urine through the kidneys, which explains the lower levels of vitamin C in diabetic patients compared with healthy patients.

So, the administration dose of vitamin C was higher than the daily dose in this study.

2.4. Administration Times for Zinc and Vitamin C Supplements during the Day

2.4.1. Administration Time of Zinc

Zinc was taken by the patient in the morning, about one hour after breakfast and morning anti-diabetic drug intake.

2.4.2. Administration Time of Vitamin C

The patients took vitamin C about 2 hours after lunch. According to the Iraqi table, these times are specified, which is characterized by a simple meal at breakfast, and the launch is the main meal.

The cause behind these separated doses was to prevent the interference between zinc and iron because vitamin C encourages iron absorption [12], while iron prevents zinc absorption [14], so the study would only be about the effect of vitamin C.

Zinc administration time ensures zinc absorption without preventing it by iron because the breakfast is

simple and is not rich in this element. Also, the patient was guided to make breakfast very simple. For that reason, their doses times were separated to avoid the prevention of zinc absorption and ensure its absorption.

3. Results

These symbols below are used for the studied groups in presenting the results: (G: A) – Diabetic patients group without foot ulcers before supplements administrations; (G: a) – Diabetic patients without foot ulcers after supplement administrations; (G: B) – Diabetic patients with foot ulcers before supplements administrations; (G: b) – Diabetic patients with foot ulcers after supplements administrations; (G: C) – Healthy control group.

3.1. Glycemic Profile Results

Table 1 shows the results of FBG, HbAIC, and insulin hormone.

Table 1 Effect of different groups in FBG, HbAIC, and insulin

Groups	Mean ± SE		
	FBG (mg/dL)	HbAIC (%)	Insulin (µIU/ml)
G: A	232.13 ± 11.40b	9.01 ± 0.31 b	36.51 ± 3.35 b
G: a	116.13 ± 3.75cd	6.51 ± 0.13 cd	14.29 ± 1.10cd
G: B	259.92 ± 12.65a	11.48 ± 0.69 a	65.80 ± 8.43 a
G: b	134.03 ± 7.20c	7.05 ± 0.24 c	19.33 ± 1.93c
G: C	89.57 ± 1.10d	5.75 ± 0.07d	6.24 ± 0.166d
LSD value	22.785 **	0886 **	9.928 **

Notes: Means marked with the different letters in the same column differed significantly;
** P ≤ 0.01

As shown in Table 1, the results were the following.

- Fasting blood glucose (FBG): FBG decreased significantly (P ≤ 0.01) after administering the supplements in both diabetic patients groups. (G: a) showed a non-significant (P ≥ 0.01) difference as compared with (G: C) while (G: b) showed a significant (P ≤ 0.01) difference in comparing with (G: C).
- HbA1C decreased significantly at (P ≤ 0.01) after administering the supplements in both patients groups. (G: a) presented a non-significant (P ≥ 0.01) difference as compared with (G: C) while (G: b) showed a significant (P ≤ 0.01) difference in comparing with (G: C).
- Serum insulin hormone: Serum insulin hormone decreased significantly (P ≤ 0.01) after administering the supplements in both patients groups. (G: a) showed a non-significant (P ≥ 0.01) difference as compared with (G: C) while (G: b) showed a significant (P ≤ 0.01) difference in comparing with (G: C).

3.2. Lipid Profile Results

Table 2 shows the results of the lipid profile.

Table 2 Effect of different groups in lipid profile

Groups	Mean ± SE					
	T. Cholesterol (mg/dL)	Triglyceride (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	ATHEROS. Index (number)
G: A	238.24 ± 4.40a	187.67 ± 9.72b	35.26 ± 1.64b	165.45 ± 4.50a	37.53 ± 1.94b	4.68 ± 0.22b
G: a	159.07 ± 7.13b	93.92 ± 4.01cd	46.55 ± 1.25a	91.99 ± 5.27b	18.79 ± 1.16cd	1.94 ± 0.15c
G: B	252.85 ± 7.88a	218.92 ± 10.24a	30.15 ± 1.34c	178.42 ± 11.03a	43.88 ± 2.17a	5.95 ± 0.45a
G: b	163.42 ± 7.99b	108.07 ± 3.84c	45.82 ± 1.05a	96.06 ± 4.95b	21.57 ± 0.94c	1.96 ± 0.12c
G: C	114.02 ± 3.92c	80.78 ± 1.89 d	48.66 ± 0.94a	50.25 ± 1.09c	16.06 ± 0.50d	1.03 ± 0.02d
LSD_value	17.519 **	19.062 **	3.751 **	15.716 **	4.137 **	0.615 **

Notes: Means with the different letters in the same column differed significantly;
** P ≤ 0.01

As shown in Table 2, the results were the following.

- Total cholesterol (TC), low-density lipoprotein (LDL), and atherosclerosis index decreased significantly at P ≤ 0.01 after the administration of the supplements in both patients groups but showed a significant (P ≤ 0.01) difference compared with (G: C).
- Triglycerides (TG) and very-low-density lipoprotein (VLDL) decreased significantly (P ≤ 0.01) after administration of the supplements in both diabetic patients groups. (G: a) showed a non-significant (P ≥ 0.01) difference as compared with (G: C), while (G: b) showed a significant (P ≤ 0.01) difference in comparison with (G: C).
- High-density lipoprotein (HDL) increased significantly (P ≤ 0.01) after the administration of the supplements in both patients groups and showed a non-significant (P ≥ 0.01) difference in comparison with (G: C).

3.3. Kidney Function

Table 3 shows the results of urea and creatinine.

Table 3 Effects of different groups on urea and creatinine

Groups	Mean ± SE	
	Urea (mg/dl)	Creatinine (mg/dL)
G: A	51.87 ± 2.11a	1.58 ± 0.10b
G: a	36.06 ± 0.58b	1.01 ± 0.04c
G: B	54.32 ± 1.01a	1.82 ± 0.13a
G: b	38.19 ± 1.45b	1.04 ± 0.07c
G: C	35.06 ± 0.65b	0.836 ± 0.02c
LSD value	3.794 **	0.230 **

Notes: Means with the different letters in the same column differed significantly;
** P ≤ 0.01

As shown in Table 3, blood urea and serum creatinine levels showed a significant decrease at P ≤

0.01 after the administration of the supplements as compared with their levels before the administrations in both patients groups and showed a non-significant ($P \geq 0.01$) difference as compared with (G: C).

3.4. Supplement Level Results

Table 4 shows supplements level results.

Table 4 Effects of different groups on zinc and vitamin C

Groups	Mean ± SE	
	Zinc (µg/dl)	Vit. C (ng/ml)
G: A	24.34 ± 1.37c	2.92 ± 0.31d
G: a	61.94 ± 1.91b	22.67 ± 2.93b
G: B	17.69 ± 2.34d	2.18 ± 0.26d
G: b	59.79 ± 3.50b	13.14 ± 1.77c
G: C	80.04 ± 1.29a	58.86 ± 0.82a
LSD value	7.522 **	4.861 **

Notes: Means with the different letters in the same column differed significantly;
** $P \leq 0.01$

As shown in Table 4, the results were the following:

- Serum zinc level increased significantly ($P \leq 0.01$) after the administration of these supplements in both patients groups but showed a high significant ($P \leq 0.01$) difference in comparison with (G: C).
- Vitamin C serum level increased significantly ($P \leq 0.01$) after the administration of these supplements in both patients groups but indicated a high significant ($P \leq 0.01$) difference in comparison with (G: C).

3.5. Blood Pressure and Urination Times

Table 5 shows the effects of different groups on systolic, diastolic, and urination times.

Table 5 Effect of different groups in systolic, diastolic, and urination times

	Mean ± SE		
Groups	Systolic (mmHg)	Diastolic (mmHg)	Urination Times (Number)
G: A	14.36 ± 0.25a	9.60 ± 0.18a	9.20 ± 0.25b
G: a	12.56 ± 0.09bc	8.53 ± 0.09bc	7.33 ± 0.12d
G: B	14.75 ± 0.21a	9.70 ± 0.16a	11.20 ± 0.39a
G: b	12.80 ± 0.13b	8.65 ± 0.10b	8.00 ± 0.20c
G: C	12.20 ± 0.08c	8.13 ± 0.10c	7.00 ± 0.16d
LSD value	0.485 **	0.397 **	0.654 **

Notes: Means with the different letters in the same column differed significantly;
** $P \leq 0.01$

As presented in Table 5, the results were the following.

- Blood pressure: both systolic and diastolic pressures decreased significantly at ($P \leq 0.01$) after administering the supplements in both patients groups. (G: a) showed a non-significant ($P \geq 0.01$) difference as compared with (G: C) while (G: b) showed a significant ($P \leq 0.01$) difference in comparing with (G: C).
- Urinations times decreased significantly ($P \leq 0.01$) after administering the supplements in both diabetic patient groups. (G: a) showed a non-significant ($P \geq 0.01$) difference as compared with (G: C) while (G: b) showed a significant ($P \leq 0.01$) difference in comparing with (G: C).

3.6. Results of Visual Acuity

Results of visual acuity of both eyes before and after zinc and vitamin C used by both diabetic patients' groups are illustrated in Tables 6 and 7.

The visual acuity results of the right eye are shown in Table 6, and those of the left eye are shown in Table 7.

Table 6 Results of the right eye

Groups	6/6	6/9	6/12	6/18	6/24	6/36	6/60	CF	HM	Total
G: A	2 (6.67%)	2 (6.67%)	20 (66.67%)	0 (0.00%)	2 (6.67%)	2 (6.67%)	2 (6.67%)	0 (0.00%)	0 (0.00%)	30 (23.07%)
G: a	20 (66.67%)	8 (26.67%)	0 (0.00%)	2 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	30 (23.07%)
G: B	0 (0.00%)	10 (50%)	5 (25%)	2 (10%)	0 (0.00%)	1 (5%)	1 (5%)	0 (0.00%)	1 (5%)	20 (15.38%)
G: b	13 (65%)	2 (10%)	2 (10%)	2 (10%)	1 (5%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	20 (15.38%)
G: C	30 (100%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	30 (23.07%)
P-value	0.0001 **	0.0001 **	0.0001 **	0.0498 *	0.108 NS	0.108 NS	0.108 NS	1.00 NS	0.549 NS	0.76

Notes: * $P \leq 0.05$;
** $P \leq 0.01$;
CF - counting fingers;
HM - hand motion

Table 7 Results of the left eye

Groups	6/6	6/9	6/12	6/18	6/24	6/36	6/60	CF	HM	Total
G: A	2 (6.67%)	12 (40.00%)	6 (20.00%)	2 (6.67%)	0 (0.00%)	6 (20.00%)	1 (3.33%)	1 (3.33%)	0 (0.00%)	30 (23.07%)
G: a	22 (73.33%)	2 (6.67%)	2 (6.67%)	0 (0.00%)	2 (6.67%)	2 (6.67%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	30 (23.07%)
G: B	1 (5%)	0 (0.00%)	9 (45%)	2 (10%)	0 (0.00%)	2 (10%)	2 (10%)	2 (10%)	2 (10%)	20 (15.38%)
G: b	9 (45%)	4 (20%)	2 (10%)	0 (0.00%)	2 (10%)	3 (15%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	20 (15.38%)

Continuation of Table 7

G: C	30 (100%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	30 (23.07%)
P-value	0.0001 **	0.0001 **	0.0001 **	0.0491 *	0.0466 *	0.0083 **	0.0471 *	0.0471 *	0.0489 *	0.076 NS

Notes: * $P \leq 0.05$;
** $P \leq 0.01$;
CF - counting fingers;
HM - hand motion

Both eyes' visual acuity improved significantly after zinc and vitamin C administration, as shown in Tables 6 and 7.

3.7. Results of Microorganisms and Antibiotic Sensitivity Tests

Results of microorganisms and antibiotic sensitivity tests from wound swabs of diabetic foot ulcers are shown in Table 8.

Table 8 Microorganisms isolated from wound swab of diabetic foot ulcer and antibiotic sensitivity tests results

Patient	Microorganism	Antibiotic sensitivity	Treatment
B1	*Candida albicans*	-	-
B2	*Klebsiella pneumoniae* *Escherichia coli*	Trimethoprims++ Amikacin s++ Nitrofurantoins+ Imipenems+	Amikacin
B3	*Staphylococcus aureus*	Levofloxacin s++ Ciprofloxacin s+	-
B4	*Staphylococcus aureus*	Levofloxacin s++ Ciprofloxacin s++ Rifampin s+	-
B5	*Staphylococcus aureus*	Levofloxacins++ Rifampin s+ Ceftriaxone s+ Gentamicin s+	Levofloxacin Rifampin
B6	*Proteus mirabilis*	Levofloxacin s++ Ciprofloxacin s++ Amikacin s+ Imipenem s+ Ceftriaxones+	-
B7	*Staphylococcus aureus*	Levofloxacin s++ Ceftriaxone s+	-
B8	*Staphylococcus aureus*	Levofloxacin s++ Nitrofurantoin s+	Levofloxacin
B9	*Klebsiella pneumoniae* *Candida albicans*	Levofloxacin s+ + Gentamicin s+	-
B10	*Staphylococcus epidermidis*	Levofloxacin s++ Clindamycin s++ Azithromycin s+	-
B11	*Staphylococcus epidermidis*	Levofloxacin s++ Azithromycin s+	-
B12	*Staphylococcus aureus*	Levofloxacin s++ Ceftriaxone s+ Nitrofurantoin s+ Gentamicin s+	-
B13	*Candida albicans*	-	-
B14	*Staphylococcus aureus*	Ciprofloxacin s++ Levofloxacin s+ Ceftriaxone s+	Ciprofloxacin
B15	*Staphylococcus epidermidis*	Levofloxacin s++ Azithromycin s++	Levofloxacin
B16	*Candida albicans*	-	-
B17	*Pseudomonas aeruginosa*	Amikacin s++ Ciprofloxacin s++ Levofloxacin s++	-
B18	*Candida albicans*	-	-
B19	*Staphylococcus aureus*	Levofloxacin s++ Ceftriaxone s+ Nitrofurantoins+	-
B20	*Klebsiella pneumoniae*	Amikacin s++ Levofloxacin s++ Azithromycin s+	Amikacin

3.8. Results of Diabetic Foot Ulcers

The patients were twenty, and the images were taken before using the supplements and periodically until they recovered, so the first image was taken before using the supplements for all the patients.

Before administering the supplements, there were no blood signs or sense in all the ulcers, as illustrated in the first images.

All the ulcers healed completely after the administration of zinc and vitamin C, without any amputation and, in most cases, without using antibiotics. Some of these cases are as follows:

3.8.1. Patient 1

The patient is a woman, 48 years old, having a foot ulcer for three days; it was infected with *Candida albicans* and recovered without using an antibiotic.

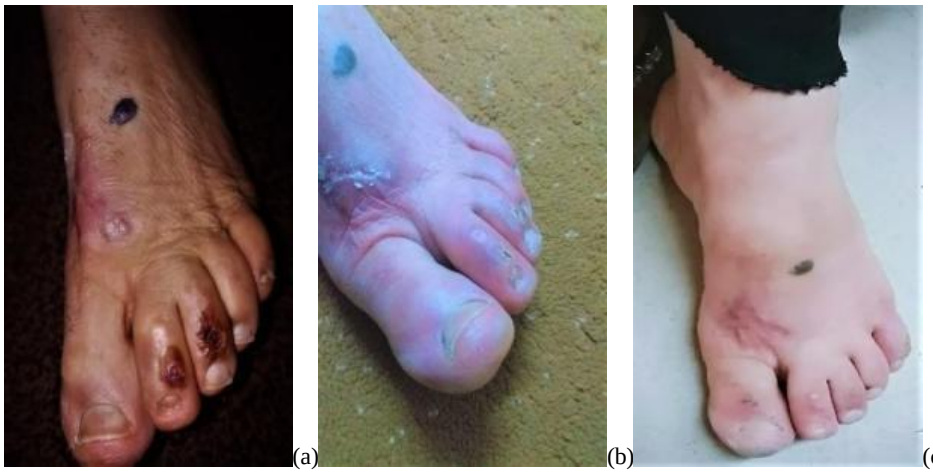

Fig. 1 (a) Before using the supplements, the color of the wound is dark brown, indicating ischemia; (b) After eight days, the healing is obvious; (c) After 14 days - complete healing, wound scars are barely visible

3.8.2. Patient 2

The patient is a man, 56 years old, having a foot ulcer for eight days. There was a mixed infection from *Klebsiella pneumoniae* and *Escherichia coli; an Amikacin* antibiotic was used in treatment. The grafting process was done. Signs of blood flow and sense appeared after four days of using the supplements.

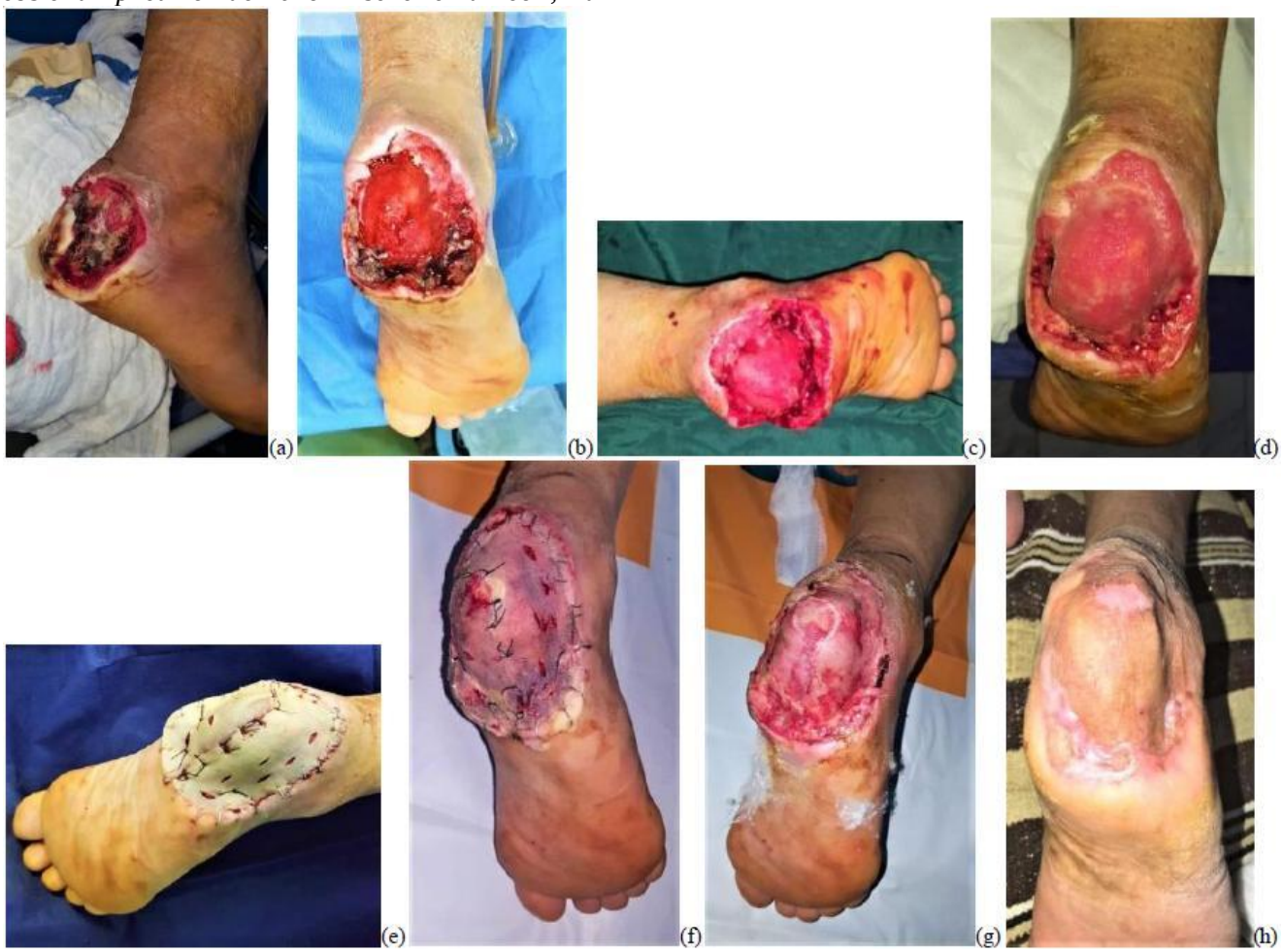

Fig. 2 (a) Before using the supplements, tissues inside the ulcer are dark brown, indicating ischemia; (b) After fifteen days - signs of blood flow, the tissue's color turned red; (c) After one month - signs of blood flow, tissue color is pink, which is considered a vital sign; (d) After two months - the healing is apparent, debridement of dead tissues; (e) After two months -tissues graft; (f) After three months, the tissues homogenized; (g) After four months, almost healed; (h) After five months, complete healing was done effectively (improvements in skin color)

3.8.3. Patient 3

The patient is a woman, 58 years old, with an ulcer after amputation; 15 days after having this ulcer, it was *Staphylococcus aureus*, recovered without using antibiotic, without graft process. However, it was required, and the tendon has appeared, which impedes it. The signs for blood flow and sense appeared after five days of using the supplements.

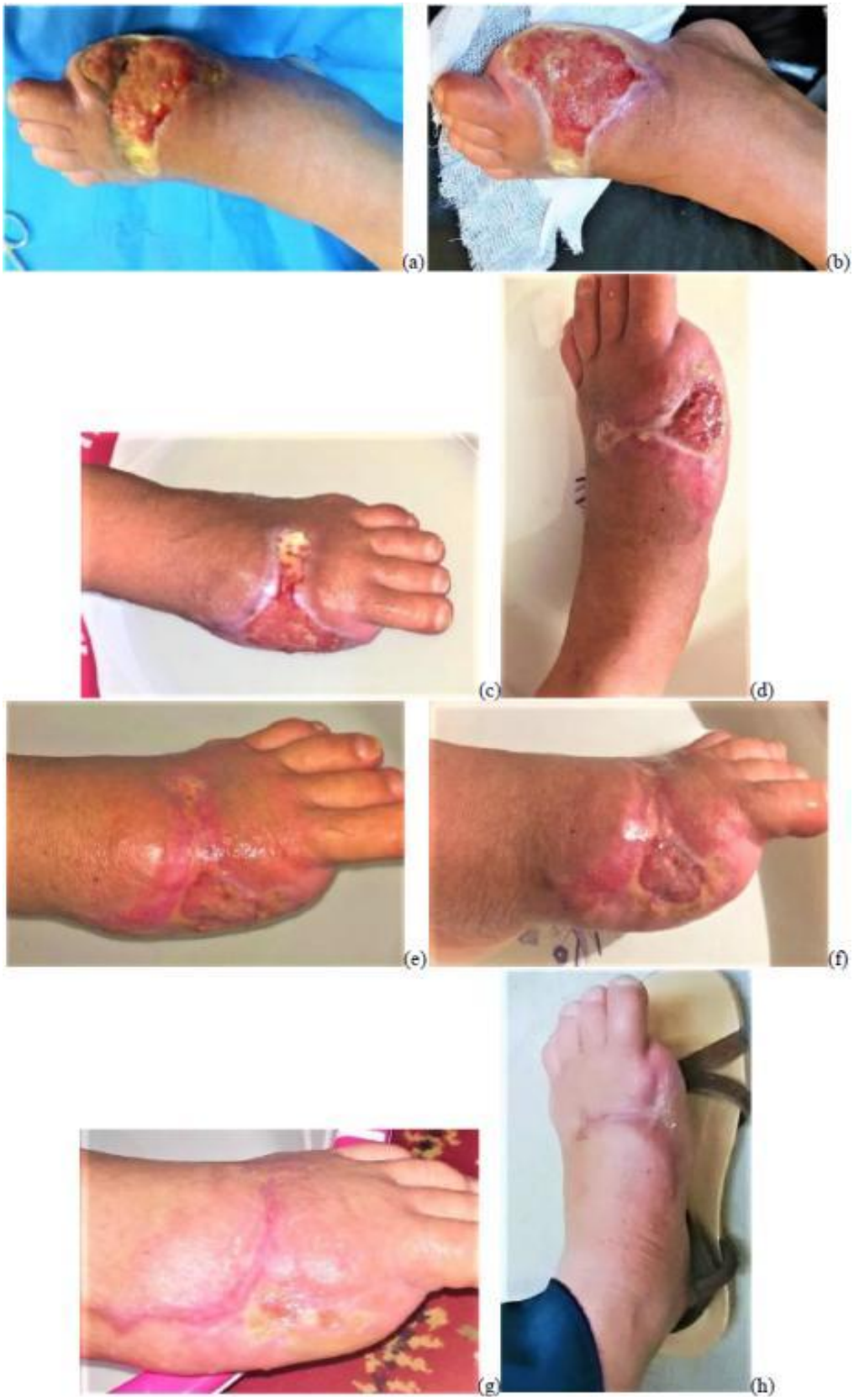

Fig. 3 (a) Before using the supplements, the skin is necrotized, and tendon appears; (b) After 10 days, blood signs are obvious; (c) After forty-five days, blood signs are apparent (the healing is visible); (d) After two months, the healing is obvious; (e) After two months and a half, the healing is obvious (the tendon is almost covered with new tissues of the skin); (f) After three months, the healing is observable (the tendon is covered completely); (g) After four months - almost healed; (h) After four months and a half - completely healed ulcer (improvements in skin color)

3.8.4. Patient 4

The patient is a man, 56 years old, having a foot ulcer for 12 days; it was infected with *Staphylococcus aureus* and recovered without using an antibiotic for less than two months. The signs for blood flow and sense appeared after four days of using the

supplements.

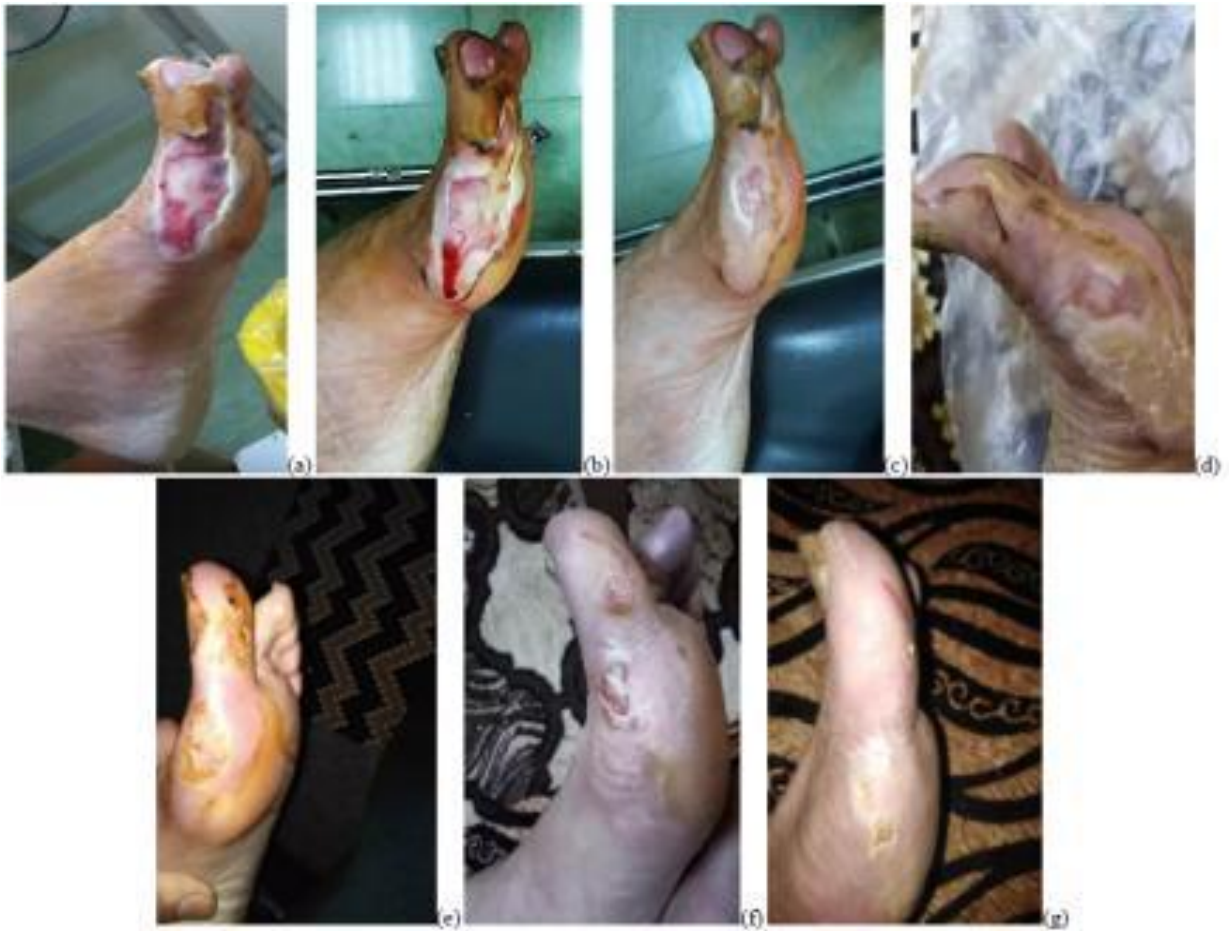

Fig. 4 (a) Before using the supplements, there was no blood flow although the ulcer was deep; (b) After four days, blood flow is obvious; (c) After ten days, the healing process is apparent; (d) After one month, tissue debridement happened; (e) After forty days, debridement is more obvious, and new tissues with healthy color are observed; (f) After fifty days - almost healing; (g) After two months - completely healed ulcer

3.8.5. Patient 5

The patient is a man, 46 years old, having a foot ulcer for five days. There was *Staphylococcus aureus.* Levofloxacin and Rifampin antibiotics were used. The foot recovered within two months.

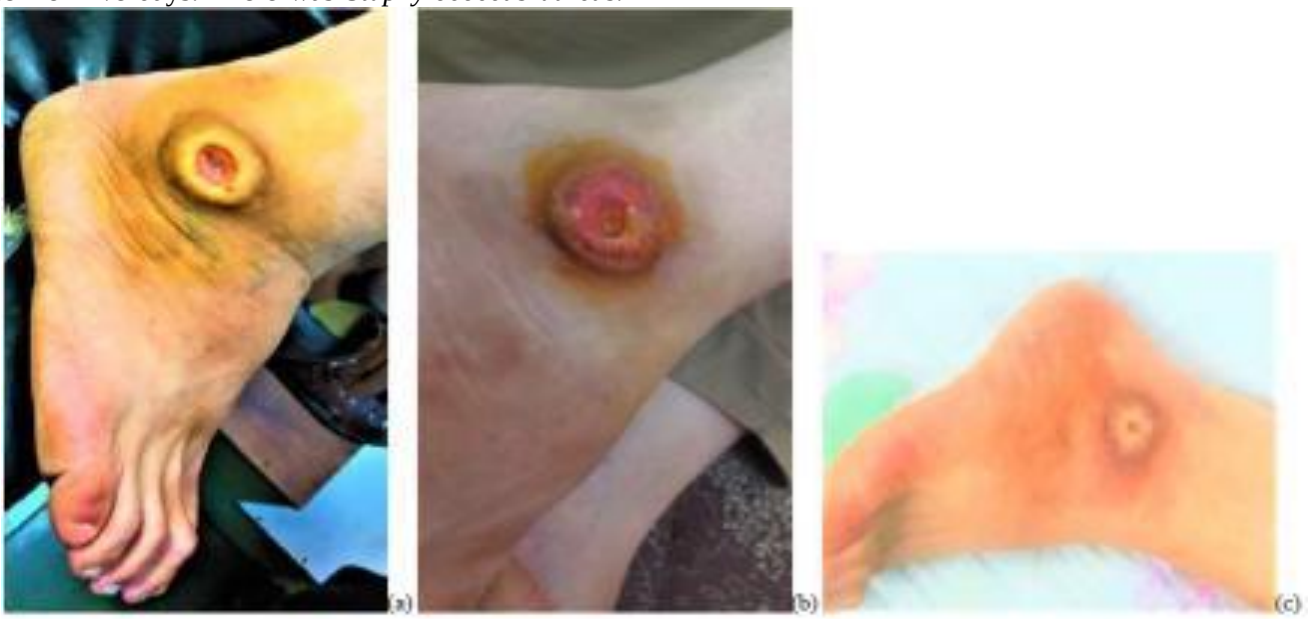

Fig. 5 (a) Before using the supplements, the ulcer was deep (surrounded area of the ulcer is pale, which is an indicator of ischemia); (b) After fifteen days, the healing process is observable, (the tissues' color is pink; it is considered a vital sign for blood flow); (c) After two months - complete healing

3.8.6. Patient 6

The patient is a man, 30 years old, having this ulcer for one month. It was *Proteus mirabilis. The foot* recovered without using antibiotics within less than one

month.

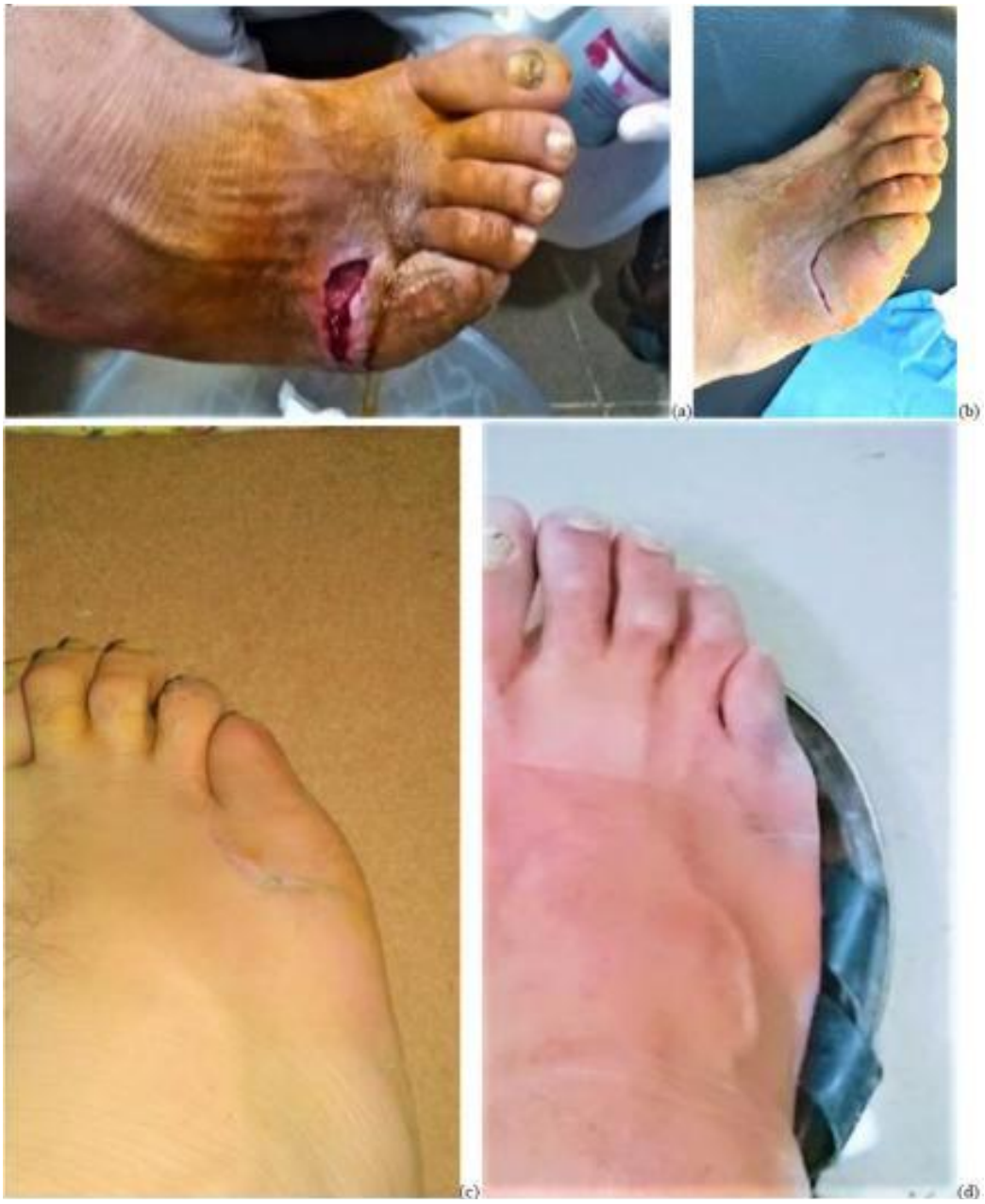

Fig. 6 (a) Before using the supplements, surrounded area of the ulcer is pale, which is an indicator of ischemia; (b) After twelve days, the healing process is obvious; (c) After one month - complete healing; (d) After two months - complete healing of the ulcer, and wound scar is barely visible

3.8.7. Patient 7

The patient is a man, 48 years old, having a foot ulcer for 20 days; the ulcer was deep and reached the bone, which caused the bone's necrosis, as illustrated in Fig. 7f. It was infected with *Staphylococcus aureus*, and Levofloxacin antibiotic was used. The signs for blood flow and sense appeared after five days of using the supplements.

Fig. 7 (a) Before using supplements, the ulcer was deep and caused necrosis in the bones (Although the ulcer was deep, there were no blood signs; surrounded area of the ulcer is pale, which is an indicator of ischemia); (b) After three days, the body rejected the necrotized bones spontaneously (They got out from the open wound - anterior and posterior view); (c) After one month, the healing process is apparent; (d) After forty-five days - almost healed; (e) After two months - complete healing (The finger became shorter than it was before, due to the rejected bones, improvement in skin color); (f) Before using the supplements, necrosis of the bones is obvious; (g) After complete healing of the ulcer - rebuilding of the necrotized bones; the finger became shorter than it was before, due to the rejected bones; (h) During using supplements - normal blood flow

During supplements use, the patient had an accident in his foot which contained an ulcer; as shown in Fig. 7h, the blood flows naturally. Before using the supplements, there was no blood sign, although the ulcer reached the bones as illustrated in the first image and x-ray image. This wound also healed completely, as illustrated in the last recovering stage image (Fig. 7e).

3.8.8. Patient 8

This patient was a man, 56 years old, having a foot ulcer for 15 days; he had two ulcers in the same foot. These ulcers appeared after amputation about two years ago; it was a mixed infection of *Candida albicans* and *Klebsiella pneumonia*, recovered without antibiotics. The signs for blood flow and sense appeared after five days of using the supplements. The foot also rejected the necrotized bone (but it is not an available image). The results are shown in Fig. 8.

Fig. 8 (a) Before using the supplements, the ulcers were dry without any blood signs. Although they were deep, skin color tended to be dark brown - ischemia was apparent; (b) After fifteen days - blood signs, improvements in skin color, debridement of dead tissues; (c) After one month, the healing process is obvious (lateral ulcers healed completely); (d) After forty-five days - almost healed; (e) After two months - completely healed ulcers, obvious improvements in skin color

3.8.9. Patient 9

A patient is a man, 55 years old, having feet ulcers for 19 days, and it was *Staphylococcus epidermidis*. He had many ulcers in his feet, which recovered without using antibiotics. The right foot is shown in Fig. 9, and the left foot is shown in Fig. 10.

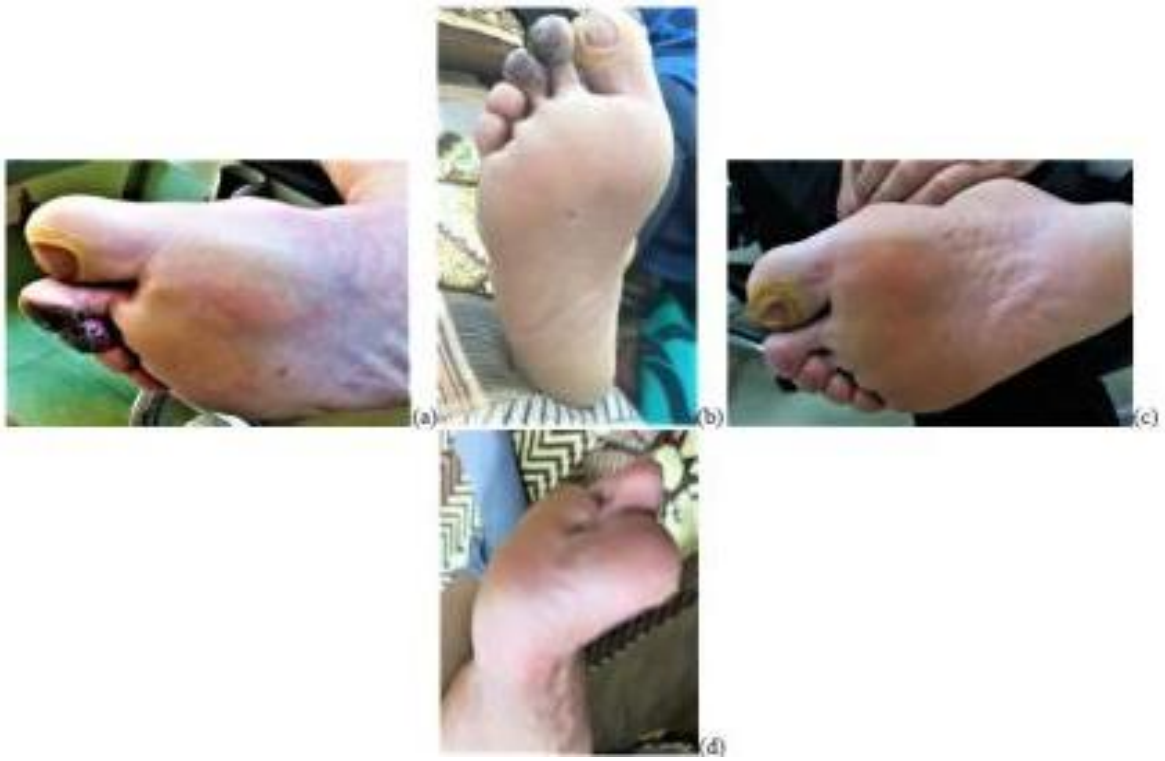

Fig. 9 (a) Before using the supplements, the tissue color is black, which is an indicator of ischemia; (b) After fifteen days, tissue color becomes brown; (c) After one month, the healing process is obvious (debridement of the dead tissues in the middle fingers); (d) After two months - complete healing

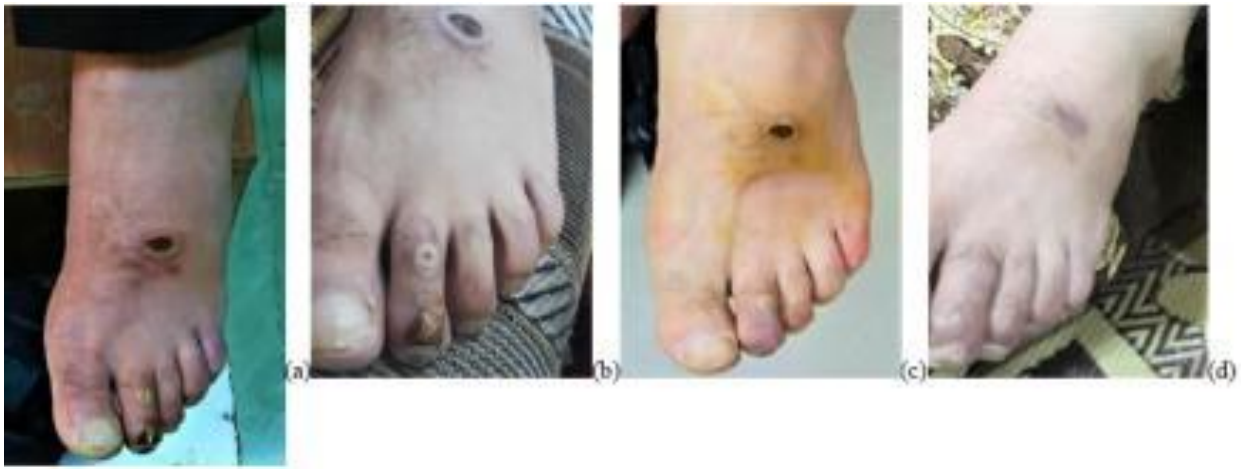

Fig. 10 (a) Before using the supplements, the upper ulcer is deep, without any blood signs (It is above a blood vessel and was infected with *Staphylococcus epidermidis*, which is considered an opportunistic bacteria), and one of the ulcers on the middle finger has black tissues; (b) After fifteen days, the upper ulcer began to heal (color turned to brown in ulcers of the finger); (c) After one month, the healing process is obvious in ulcer of the finger (debridement of dead tissues); (d) After two months - complete healing of all the ulcers

4. Discussion

This study revealed the improvement effects of zinc and vitamin C on insulin, FBG, HbA1C, lipids profile, blood urea, and serum creatinine. These effects result from the synergistic and complementary influence of zinc and vitamin C on many physiological functions.

Zinc affects the metabolism of macronutrients (i.e., carbohydrates, fats, and proteins). These effects arise because the metabolic activity of 300 enzymes in the body requires zinc to function properly. These enzymes are closely involved in the metabolism of carbohydrates, fats, and proteins [9]. Moreover, zinc has many effects on insulin.

For decades, researchers have recognized a physical–chemical relationship between insulin and zinc [11]; zinc's effects on insulin include the following:

- Insulin synthesis: Zinc is required for insulin synthesis because insulin is secreted by zinc-insulin crystals [32]. Zinc has a regulatory role in insulin production; reduced zinc levels lead to reduced insulin production [11]. Insulin production and effective storage within vesicles are carefully related to zinc transport into β-cells [29].
- Insulin release and transport: Zinc plays an important role in insulin release and transport [5].
- Serum insulin levels: Zinc increases serum insulin by about 70% [29].

- Insulin storage: Zinc is vital for storing and processing insulin in the body [5]. Zinc's binding to insulin is significant for insulin hormone crystallization. Researchers have posited that the two zinc ions lying at the center of each hexameric insulin unit ensure that adequate insulin quantities can be stored in pancreatic β-cells to allow sufficient release after meals [10].
- Insulin sensitivity: Zinc increases insulin sensitivity by increasing insulin's capability to bind to its receptors [11]. Zinc improves antidiabetic activity and raises glucose uptake by hepatic and muscle cells [33]. It has been shown to stimulate phosphorylation of the IR-ß (insulin receptor) subunit [29].

In skeletal muscles, Zinc-α2-glycoprotein stimulates AMP-activated protein kinase (AMPKα) phosphorylation and increases cellular GLUT4 protein. This increase in GLUT4 expression has also been observed in adipose tissue, resulting in glucose uptake [29].

Low serum levels of zinc are associated with diabetes and elevated insulin resistance [10]. Zinc deficiency may aggravate insulin hormone resistance in non-insulin-dependent diabetes mellitus (NIDDM) [1]. Some investigators have considered that zinc supplementation could improve insulin sensitivity in type 2 DM [33]. Therefore, zinc could explain the high insulin hormone levels and insulin resistance in diabetic patients before using the supplements and the decreases in these levels after using them.

- Insulin's conformational integrity. Zinc plays a clear role in insulin's conformational integrity in the hexameric form [33]. It plays a significant role in forming insulin crystals [5] and preserves insulin's structural integrity [32]. Zinc is required for insulin's hexamerization and its conversion from proinsulin to insulin in the Golgi apparatus; therefore, an adequate amount of zinc must be imported to this compartment [34]. Zinc ions that are co-secreted with insulin suppress monomeric insulin's inherent amyloidogenic properties [6].

Therefore, zinc's role related to insulin can be considered the main reason for diabetes mellitus occurrence. Zinc has an important role in the normal functioning of the pancreas's islet cells. Notably, β-cells and their granules are extremely rich in zinc [29], and decreased zinc levels affect the islet cells' ability to produce and secrete insulin hormone, which might compound the problem, particularly in type 2 diabetes mellitus [33]. Zinc deficiency leads to elevated blood sugars and weakened abilities to synthesize and secrete insulin, as well as to use glucose [11].

In diabetic patients, zinc levels are abnormally low in the pancreas. Low zinc levels in the blood plasma affect the ability of the islets of Langerhans to produce and secrete insulin [5]. One study revealed that mice with zinc deficiency had reduced numbers of insulin granules in their pancreatic β-cells, as well as impaired glucose-stimulated insulin secretion (GSIS) [34].

In addition to zinc's effects on insulin, the pituitary growth hormone–insulin-like growth factor-1 axis responds to zinc [10]. Thus, zinc has two functions with the same effects. These effects on insulin synthesis, storage, release, transport, and sensitivity improve insulin's functional efficiency. Therefore, all these improvements affect the metabolism of macronutrients and vitamin C, which are discussed in the following sections.

4.1. Carbohydrate Metabolism

Insulin principally increases glucose's facilitated transport into cells, which lowers blood glucose. Insulin acts on hepatocytes to elevate blood glucose's mobilization into the muscle cells and fat tissues, maintaining blood glucose within normal levels [4, 12].

Insulin's action in lowering blood glucose was improved by micro-minerals such as zinc, chromium, and selenium. As cofactors for many metabolism-related enzymes, mainly those related to glucose metabolism [11], these micro-minerals stimulate insulin receptors and performance.

At the biochemical level, insulin has the following effects:

- A stimulatory effect on glycolytic enzymes (glucokinase; phosphofructokinase; fructose 2,6 bisphosphatase; and pyruvate kinase).
- An inhibitory effect on the gluconeogenic enzyme phosphoenolpyruvate kinase [12].

Moreover, zinc has similar effects on insulin; zinc is recognized as inhibiting gluconeogenesis and stimulating glycolysis, an effect that is not overcome by presence of glucagon. In vitro studies have confirmed that zinc increases the activity of glycolytic enzymes pyruvate kinase (PK), and phosphofructokinase (PFK) in a concentration- and time-dependent manner [29].

- Promotion of glycogen synthesis in the liver [18].

Therefore, insulin's effects on glucose metabolism lead to the following results:

A. Increased facilitated transport of glucose into cells

B. Increased glycolysis and decreased gluconeogenesis

C. Increased glycogen synthesis

Hence, increased utilization of glucose decreases blood glucose.

Studies [1, 5, 29] have demonstrated that zinc plays a role in glucose metabolism and glycemic control by reducing fasting blood glucose and glucose tolerance, so the mechanism of its effect lies in its influence on insulin. Moreover, urination frequency decreased due to decreased blood glucose levels. Increasing urination (polyuria) is a diabetes mellitus characteristic. That

results from the increased glucose levels in the urine, which affects losing water from the body [20].

4.2. Lipid Metabolism

Insulin has an essential role in lipid metabolism regulation and is involved in the following processes:

- *Lipase:* In the adipose tissues, insulin inhibits hormone-sensitive lipase. Therefore, insulin has antilipolytic effects, stimulates triglyceride storage in adipocytes, and decreases releasing of free fatty acids from adipose tissues into blood flow [35].
- *VLDL:* Normally, insulin suppresses VLDL creation by controlling influxes of substrates for liver TG synthesis [36].
- *Triglyceride:* Insulin is a powerful activator of lipoprotein lipase (LPL), stimulating the catabolism of triglyceride-rich lipoproteins and decreasing plasma triglyceride levels [35].
- *LDL:* insulin promotes LDL clearance by increasing LDL-receptor expression and activity [37].
- *HDL:* Insulin acts on the metabolism of HDL by activating Lecithin Cholesterol AcylTransferase (LCAT) and hepatic lipase activities [35].

Zinc-α2-glycoproteins are involved in lipid metabolism, which affects the expression of many lipolytic enzymes at the hepatic and adipose tissue levels. Zinc-α2-glycoproteins increase the expression of adipose triglyceride lipase, hormone-sensitive lipase, and lipolytic enzymes in the white adipose tissues [29]. Hence, zinc has the same effects as the insulin hormone on lipid metabolism, leading to a decrease in lipid levels in the blood. Insulin increases fatty acids and triglyceride synthesis, thus increasing fat storage (adipogenesis). Since insulin functions are anabolic [18], it is considered a fat-preserving hormone.

While the high levels of lipids in diabetic patients before using the supplements result in diabetes, the abnormalities in the lipid profile are predominant in diabetes mellitus due to insulin resistance or deficiency, impacting key enzymes and pathways in lipid metabolism [22]. This is also a result of zinc deficiency. Low serum levels of zinc were associated with the increased occurrence of diabetes, such as hypertriglyceridemia, whereas the presence of zinc prevents lipid peroxidation; therefore, zinc plays a significant role in protecting the cells from oxidative stress [29].

Also, vitamin C has also shown restorative effects on lipids profile as it significantly contributes to the treatment of atherosclerosis in type 2 diabetic patients [12]. Vitamin C inhibits low-density lipoprotein oxidation and helps decrease cholesterol levels by converting the cholesterol into bile acid [13].

These effects lead to storage of fatty acids in the adipose tissues, thus reducing triglycerides and VLDL, as well as cholesterol, LDL, and atherosclerosis index levels.

Triglycerides and VLDL levels decreased and reached normal values after the administration of zinc and vitamin C. Triglycerides are considered the second line of energy in the body. They are stored in the body as adipose tissues by the action of the insulin hormone and utilize the first line of energy (glucose), which can enter the cells through insulin hormone action, which is improved by the action of zinc. As VLDL are triglyceride transporters, their levels depend on triglycerides levels, so they are also decreased.

Although total cholesterol, LDL, and atherosclerosis index levels decreased, they were not within normal levels. These lipids levels depend on insulin hormone action and other factors such as age, nutrition, genetics, and physical inactivity [38]. Also, liver activity converts cholesterol into bile acids [39].

Excessive oxidation of fatty acids interferes with insulin-mediated glucose uptake by the muscle cells [23]. Therefore, it can be concluded that increases in blood lipid levels also increase blood glucose levels. Further, high blood glucose levels contribute to higher LDL and lower HDL [38], meaning that both glucose and lipids levels affect each other. For this reason, diabetes mellitus is considered a progressive disease [26].

4.3. Protein Metabolism

Insulin functions, which are anabolic, stimulate the transport of free amino acids to the liver and muscle cells for protein synthesis. Hence, insulin inhibits the catabolism of proteins [18].

Given that the insulin hormone is considered a protein-preserving hormone, proteins are considered the third line of energy in existence and allow glucose to enter cells by insulin hormone efficiency and sufficiency due to the effect of zinc. Since there is no need to use proteins in energy generation or precursors for gluconeogenesis, these effects lead to utilization and storage of amino acids in the cells and tissues. This action has many effects:

- Normal functions of many enzymes in cells, including DNA synthesis and protection of cells from apoptosis;
- Construction and repair of any damaged tissues;
- Protection of many tissues and organs from damage, such as eyes, kidneys, nerves, and heart;
- Decrease in blood creatinine and urea.

In addition to the effects of zinc on the insulin hormone in improving its function to regulate protein metabolism, zinc also improves key antioxidant enzymes and proteins [29]. Zinc also protects the proteins from proteolysis, which is caused by the inactivation of those enzymes and proteins.

An increase in blood urea and creatinine levels before using supplements is the result of diabetes mellitus due to insulin hormone inefficiency. Therefore, it can be concluded that the role of zinc in improving blood glucose, lipids, urea, and creatinine

levels occurs in three mechanisms:

- Its effect on the metabolic activity of 300 enzymes in the body, all of which are closely involved with the metabolism of carbohydrates, fats, and proteins;
- Its effect on the insulin hormone;
- Its effect on the pituitary growth hormone insulin-like growth factor-1 axis.

Also, the metabolism of macronutrients such as carbohydrates, lipids, and proteins are connected and affect each other.

4.4. Vitamin C Metabolism

Vitamin C is dependent on the insulin hormone to enter the cells. Both (glucose and ascorbate) require help from the insulin hormone before they can penetrate the cell membranes using special pumps [12]. Hyperglycemia from diabetes mellitus could inhibit the entry of dehydroascorbic acid into RBCs [40]. Hence, when the insulin hormone is sufficient and efficient, vitamin C can enter the cells. Vitamin C and glucose compete to enter the cells [12], which results in a decrease in fasting blood glucose and causes more vitamin C to enter the cells. Megadoses of vitamin C in type 2 diabetes mellitus help to decrease blood glucose [12]. The effects of simultaneous Vitamin C entry into the cells with zinc availability in the body have the following effects.

4.4.1. More Nitric Oxide Bioavailability

Nitric oxide (No) bioavailability increases by the action of vitamin C [41], which in the insulin action allowing vitamin C to enter the cells [12].

Long-term vitamin C treatment increases nitric oxide synthase activity and vascular tetrahydrobiopterin levels [42]. Vitamin C improves endothelium-dependent relaxation because of increased nitric oxide bioavailability [41]. Zinc is well-known to activate the C peptide, which results in increased energy utilization in the red blood cells and the release of (ATP), which, in turn, stimulates (NO) production in the endothelium and platelets, causing a reduction in platelet activity [29]. The endothelial cells take up zinc ions rapidly, perhaps through the endocytosis of albumin-bound zinc, which is the largest pool of bound zinc in plasma [10]. Therefore, nitric oxide (NO) synthesis requires vitamin C and zinc elements. These improvements in nitric oxide production lead to normal endothelial functions.

4.4.2. Normal RBC and Platelets

Hyperglycemia in diabetes created lower RBC ascorbate with increased RBC rigidity, which is a candidate to drive microvascular angiopathy because Hyperglycemia from diabetes mellitus could inhibit entry of dehydroascorbic acid into RBCs. RBC deformability is connected to RBC osmotic fragility [40]. Zinc deficiency increases the osmotic fragility of the erythrocyte membranes [10], while zinc increases energy utilization in the red blood cells [29]. Zinc deficiency creates impaired hemostasis because of defective platelets aggregation [10]. Also, NO can inhibit platelet aggregation [42].

Decreasing blood glucose levels, zinc availability, and vitamin C entry to RBCs help in normal RBCs, which results in lower HbA1C levels. Zinc supplementation improves glycaemic control by reducing HbA1C in diabetic patients [5, 29].

Also, vitamin C reduces glycosylated hemoglobin (HbA1C) [12]. As a result, HbA1C levels decreased after zinc and vitamin C administration.

In the diabetic state, fragility and deformability of RBCs are caused by zinc deficiency and vitamin C inability to enter RBCs. They increase glucose adhesive, which is high due to insulin dysfunction caused by zinc deficiency in the RBCs. That leads to high HbA1C levels, hence increased RBC rigidity, with the potential to drive microvascular angiopathy, reducing RBCs' passing through the small capillaries nourishing the farthest tissues such as those of feet. That results in less oxygen, which causes ischemia and diabetic foot ulcer.

4.4.3. Health Prostaglandin and Normal Blood Clotting

Zinc is essential to prostaglandin production and blood clotting [9].

4.4.4. Less Glycosylation of Proteins

Persistent hyperglycemia gives rise to spontaneous non-enzymatic glycosylation of the proteins, which causes the glycosylation of all proteins, resulting in the basement membrane thickening, particularly of small blood vessels (microangiopathy), and glycosylation of collagen cross-linking and the matrix proteins of arterial walls. It finally causes endothelial cell dysfunction, which contributes to atherosclerosis leading to diabetic complications such as nephropathy, retinopathy, and neuropathy [11].

Decreased blood glucose, more protein synthesis, and less protein proteolysis, resulting from normal insulin functions due to zinc available, lead to decreased protein glycosylation. Also, vitamin C in type 2 diabetes mellitus helps to decrease glycosylation [12]. Less glycosylation leads to less thickening of the basements membrane, resulting in more elasticity in the blood vessels, ensuring normal blood flow.

4.4.5. Improvements in Capillary Strength

Megadoses of vitamin C in DM2 decrease capillary fragility in diabetic patients [12].

4.4.6. Zinc and Vitamin C Roles in Decreasing Oxidative Stress Associated with Diabetes Mellitus

Vitamin C (VC) is the most effective water-soluble

antioxidant in the cell membranes and plasma. It could have protection from free radicals especially scavenging superoxide radicals. Also, VC reduces oxidative stress [41, 43]. It provides an antioxidant effect that limits tissue injury generated by inflammatory cells. It combats the damage of free radicals by neutralizing hydroxyl and superoxide radicals [15, 12]. Also, Vitamin C is well-known to contribute to the regeneration of the antioxidants molecules such as carotenes, glutathione, tocopherol, and urate [13]. So vitamin C contributes to antioxidant action directly and indirectly.

Many preclinical studies in ischemia/reperfusion, sepsis, and trauma models indicate that vitamin C administrated in pharmacological doses weakens inflammation and oxidative stress, and restores endothelial and organ function [31].

Long-term zinc deprivation renders the organism more susceptible to injury induced by oxidative stress. Zinc plays a significant role in protecting the cells from oxidative stress [10]. Various studies show that people with small antioxidants have an increased risk of diabetes complications [2].

Zinc and vitamin C are considered protective factors for their powerful antioxidant characteristics. They have protective effects on internal injuries caused by oxidative stress, which results from utilizing fatty acids as an energy source instead of glucose, which cannot enter the cells due to insulin hormone dysfunction in diabetic patients. Fatty acids generate more energy and depend completely on aerobic analysis [44]. This process requires more oxygen; hence, more reactive oxygen species (ROS) are produced, making the cells and tissues more susceptible to internal cell injury. Also, ROS decreases the bioavailability of nitric oxide (NO) in the endothelium by reacting chemically with NO to produce peroxynitrite (ONOO-) [27], which results in endothelial dysfunction, leading to diabetic complications, whereas vitamin C stabilizes the endothelium and improves endothelial function. It reduces vascular inflammation and vascular oxidative stress. Also, it improves redox balance. Vitamin C enhances endothelium-dependent relaxation because of increased nitric oxide bioavailability. It improves eNOS- dependent vascular reactivity. Also, it prevents apoptosis in cultured endothelial cells [13, 15, 41].

All these improvements lead to normal endothelial functions, decrease glucose and lipids levels in the blood. They also store and utilize amino acids. These factors decrease blood viscosity, which increases blood velocity, resulting in normal blood flow, whereas diabetic patients with and without complications have unique peripheral blood flow characteristics [45].

The blood flow in a diabetic patient was observed while drawing blood during a checkup. Before zinc and vitamin C were administered, the blood was pulled hardly and clotted in the syringe, while after that, the blood began to flow normally.

All these factors ensure the normal function of blood vessels that supply efficient and sufficient blood flow to active tissues and organs which are requiring continuous blood flow, such as nerves, eyes, kidneys, liver, and heart. It also supplies the farthest tissues, such as those in the feet. For these reasons, diabetes mellitus complications decreased after administration of zinc and vitamin C, including complete healing of diabetic foot ulcers, improvements in kidney functions, blood pressure, and visual acuity, whereas diabetes mellitus is usually related to hypertension [3].

The improvements in the visual acuity of the eyes after administration of zinc and vitamin C resulted from normal blood flow, in addition to high concentrations of zinc found in the eye's retina. Existing evidence connects zinc deficiency and deteriorating vision associated with aging [9]. Vitamin A (an antioxidant) is dependent on sufficient zinc levels for its release from the site of storage in the liver and metabolism [1]. Vitamin A has been purported to have a significant role in the function of retinal photoreceptors [46]. So, zinc has direct and indirect effects on visual acuity.

Studies [10, 11] mentioned the zinc role in decreasing diabetic complications by increasing zinc-dependent antioxidant enzymes, which decrease free radicals that protect tissues and peripheral organs from damage and decrease these complications.

Moreover, studies [12, 13] confirmed that vitamin C reduces diabetic microvascular complications, such as retinopathy, nephropathy, and diabetic foot ulcer.

4.5. Diabetic Foot Ulcer

Before using the supplements, there were no vital signs from nerve sensation or blood flow in almost patients at the beginning of the study. The foot was dry and squeezed strongly to obtain a sample for culture; this sample was only pus without any sign of blood; although the wound was open and deep during that, the patient had no sense of the foot. However, it was squeezed forcefully, while, after about 3-5 days, the patients had a sense in the foot when it was touched, and it caused pain; the blood began to flow.

4.5.1. The Wound Healing

There was complete healing of the ulcers. The normal blood flow ensures that nutrients and immune cells reach the tissues, which leads to normal wound healing and normal defense against foreign germs.

Some patients had a tissue debridement in the foot, resulting from zinc action. It has several actions that may promote debridement and wound healing because zinc is vital for cell division and the synthesis of DNA and proteins. Zinc is also critical to tissue growth, including connective tissue growth and wound healing, while zinc deficiency causes delayed healing of the wounds [9].

Vitamin C plays a significant role in maintaining skin health. It increases collagen fibers and helps in

collagen production and stabilization. In addition, it can promote keratinocyte differentiation which is important in the integrity of the skin barriers and significantly prevents skin water loss [47]. Also, the human body has many zinc-dependent enzymes that promote collagen synthesis, so it aids in wound healing [9]. Therefore zinc and vitamin C have complementary effects on wound healing.

The damaging effects of oxidative stress are primarily caused by the creation of free radicals of oxygen and reactive oxygen species (ROS) [2]. ROS causes organ damage, necrosis, and ultimately death [12], common and related to a diabetic foot ulcer. However, these substances are modifiable by the action of enzymatic antioxidants, such as superoxide dismutase (SOD) or non-enzymatic antioxidants [2]. Vitamin C is one of the naturally occurring antioxidants [12]. Zinc also has antioxidant characteristics [29]. So, zinc and vitamin C improve the healing process and protect the tissues from damage by ROS.

4.5.2. Antibiotic and Diabetic Foot Ulcers

In this study, most of the patients were treated without antibiotic use. Improvements in blood flow, done by using vitamin C and zinc, ensured that immune cells reached the infected foot ulcers and helped resist pathogens and heal the ulcers. Antioxidant nutrients, such as vitamin C and zinc, improve various immune functions by playing an important protective role against infections caused by bacteria, viruses, and parasites. As a result, they have been associated with modulating the host's resistance or susceptibility to infectious pathogens [10].

The body's B cells are dependent on zinc for proliferation; they do so to a lesser extent than T cells. A heightened level of apoptosis in pre-B and T immune cells has been found to exist in zinc-deficient mice. Zinc deficiency has a diminishing effect on T cells' functioning. Thymulin, a hormone secreted by thymic epithelial cells, requires zinc as a cofactor and exists in the plasma in two forms: a zinc-bound active form and a zinc-free inactive form. It is vital for T cells' differentiation and function [10]. Zinc is critical to the immune system's functioning [9], while a zinc deficiency generates impaired hemostasis because of a decrease in T cell numbers and a reduced response of T-lymphocytes to phytomitogens. Zinc is the only naturally occurring lymphocytic mitogen [10].

Vitamin C can improve the immune system's protective mechanism and is necessary to improve resistance against infection in wounds that accelerate the wound healing process [13, 43]. It further improves lymphocyte function and reduces bacteriological activity [12].

4.5.3. Nerve Sensation

In this study, the effects of using vitamin C and zinc were noted by improvements in endothelial function, blood vessel function, blood cell function, and blood flow. All those lead to improvements in nerve function and sensation, which were noted by the patients when their feet were touched. Before using the supplements, the patients could not feel any sensation in their feet when a sample was collected for culture, even when the foot was squeezed, whereas, after using them, the patients could feel the pain in the foot ulcers due to the deep wounds when they were touched.

Zinc modulates cellular signal transduction processes and functions as a modulator of synaptic neurotransmission, as shown in zinc-containing neurons in the forebrain [10].

Vitamin C influences the nervous system and chronic illnesses [48]. It has been widely used to treat neurodegenerative diseases [13].

4.5.4. Bone Rebuilding

There were two patients with necrotized bones due to ulcers in this study. After about three to five days, their bodies rejected the necrotic bones and began to rebuild them. Vitamin C is necessary for synthesizing and keeping bones, cartilages, and tendons healthy [43]. It encourages the growth, development, and maintenance of osteoblasts and delays osteoporosis [12].

Zinc is essential to connective tissue growth and bone mineralization [9]. Zinc supplementation has been demonstrated to prevent bone loss in rats with chronic type 1 diabetes mellitus by stimulating the mineralizing phenotype in osteoblasts and reducing the resorptive phenotype in osteoclasts [29].

So, feet became protected from amputation after using the supplements (zinc and vitamin C), which are common and the most predominant among diabetic foot ulcer patients, because there were improvements in blood flow and nerve sensation. Also, glucose levels began to decrease. In addition, the wound began to heal after using the supplements. That means the problems facing the patient and leading to amputation were resolved, and the patient returned to a normal state.

4.6. Zinc and Vitamin C Levels before and after Administration

4.6.1. Serum Zinc Level

Serum zinc levels before the administration were significantly low within deficiency levels. Zinc levels in serum are reduced in both Type 1 and Type 2 diabetes mellitus because of zinc loss due to excessive urination [5, 10, 11]. It is related to increased levels of (oxidative damage), including increased lipids, proteins, and DNA oxidation [10].

After the administration, the zinc level increased significantly but did not reach the normal level. Diabetes is described by a pro-inflammatory state, which leads to oxidative stress that produces free

radicals [13]. As zinc has antioxidant characteristics [29], it is more consumed by diabetic patients. Also, zinc is a water-soluble element, and it is not stored effectively in body tissues [9].

4.6.2. Vitamin C Serum Level

Before the administration, the levels of vitamin C were excessively lower than the normal because, structurally, vitamin C is similar to glucose. Therefore, it may compete with glucose for transportation into the cell. During hyperglycemia, uptake of vitamin C into the cells is impaired [12]. As vitamin C is water-soluble [43], it will be excreted in the urine through the kidneys. For these reasons, its level is very low in diabetic patients.

After the administration, vitamin C levels increased significantly. However, they did not reach the normal range due to diabetes described by a pro-inflammatory state, which leads to oxidative stress that produces free radicals [13, 19]. Vitamin C is a powerful dietary antioxidant [12]. So it is more consumed by diabetic patients.

Also, increased requirements and decreased vitamin C intake in the body [31]. In addition to biological viability of vitamin C decreases over time [12].

Except for the cases whose FBG and other parameters became normal, their zinc and vitamin C levels increased and became at normal levels.

4.7. Diabetic Drugs

At the beginning of the supplement administration, the diabetic drugs were not stopped or modified because it was not expected that these supplements would decrease blood glucose and become with or near to normal levels. However, until hypoglycemia states appeared, random blood glucose was about (70 mg/dL) at some times with some patients, especially those treated with insulin hormone therapy, so diabetic drugs began to modulate:

- Insulin hormone therapy is stopped with all the patients who were treated with it;
- Other diabetic drugs began to reduce, one time instead of three times;
- Some patients stopped their drugs, and their blood glucose became normal.

Decrease in blood glucose hypoglycemia states happened and reached 70 mg/dL with patients depending on insulin hormone therapy. They are considered not severe due to the zinc role in glucagon secretion. During hypoglycemia, the principal signal that initiates glucagon secretion could be detected by α-cells. A sudden zinc decrease parallels the insulin hormone drop in the islet periportal circulation. This drop of zinc concentration closes α-cells ion channels, promoting the entry of calcium that stimulates glucagon secretion [29].

In some studies that included the administration of vitamin C alone, FBG did not decrease significantly. Only the RBS decreases for hours; this results from vitamin C entry into the brain cells competing with glucose. Glucose uptake into neurons mainly happens via insulin-independent glucose transporter channels (GLUT1, 2, and 3) [30]. In this study, it has a role in decreasing fasting blood glucose by competing with it and supporting zinc's role in improving insulin hormone functions.

5. Conclusion

5.1. Zinc Element and Vitamin C Roles

Zinc element and vitamin C have vital roles in treating diabetes mellitus and its complications.

Zinc has many physiological effects, which are:

1. Zinc affects the metabolic activity of 300 enzymes in the body. These enzymes are involved closely with the metabolism of carbohydrates, fats, and proteins;
2. Zinc affects insulin hormone in many aspects.

The effects of zinc on insulin hormone are:

A. Insulin synthesis;
B. Insulin release and transport;
C. Improvements in serum insulin levels;
D. Insulin storage;
E. Sensitivity of insulin;
F. Insulin conformational integrity.

These effects on insulin synthesis, storage, release, transport, and sensitivity improve insulin function efficiency. They also affect the metabolisms of macronutrients (carbohydrates, fats, and proteins) and vitamin C.

5.1.1. Carbohydrate Metabolism

Carbohydrates metabolism improvements decrease blood glucose, glycated hemoglobin levels, and urination times.

5.1.2. Lipid Metabolism

Lipids metabolism improvements lead to improvements in lipids levels in the blood.

5.1.3. Protein Metabolism

Proteins metabolism improvements lead to:

- Normal functions of many enzymes in the cells, including DNA synthesis, protect the cells from apoptosis.
- Help in building and repairing many damaged tissues such as foot ulcers;
- Protect many tissues and organs from damage, such as eyes, kidneys, nerves, and heart;
- Decreasing blood creatinine and urea.

3. Zinc has effects on the pituitary growth hormone-insulin-like growth factor-1 axis.

So it can be concluded that zinc's role in improving blood glucose, lipids, urea, creatinine levels, and foot ulcer occurs in three mechanisms:

- Its effect on the metabolic activity of 300

enzymes in the body which are involved closely with the metabolism of carbohydrates, fats, proteins;

- Its effects on insulin hormone;
- Its effect on the pituitary growth hormone-insulin-like growth factor-1 axis.

5.1.4. Vitamin C Metabolism

Vitamin C is dependent on the insulin hormone to enter cells. When insulin is sufficient and efficient, vitamin C can enter the cells and accomplish its functions.

The entry of Vitamin C into the cells while zinc is available in the body has many positive effects:

a) More nitric oxide bioavailability: improvements in nitric oxide production lead to normal endothelial functions;

b) Normal RBC and platelets, which decrease HbA1C;

c) Healthy prostaglandin and normal blood clotting;

d) Less glycosylation of proteins;

e) Improvements in capillary strength;

f) Decrease of oxidative stress associated with diabetes mellitus due to vitamin C and zincs' powerful antioxidant characteristics.

Vitamin C and zinc protect the body from internal injury caused by oxidative stress, which results from utilizing fatty acids as an energy source instead of glucose, which cannot enter the cells due to the dysfunction of the insulin hormone. Fatty acids generate more energy and depend completely on aerobic metabolism, and therefore, require more oxygen. Hence, more reactive oxygen species (ROS) are produced, making the body's cells and tissues more susceptible to internal cell injury.

All the effects brought about by the interaction of vitamin C and zinc in the body lead to normal endothelial functions as well as the decrease of glucose, improvement of lipid levels in the blood, and the storage and utilization of amino acids. All these factors decrease blood viscosity which, in turn, increases blood velocity and results in normal blood flow; thus, normal blood vessel functions are ensured, blood flows efficiently and sufficiently to active tissues and organs which require continuous blood flow, such as the nerves, eyes, kidneys, liver, and heart. Because vitamin C and zinc were ingested, diabetes mellitus complications decreased, including the complete healing of diabetic foot ulcers, improvements in kidney functions, blood pressure, and eyesight.

Therefore, it can be concluded that zinc and vitamin C play important roles in regulating the abnormal physiological functions resulting from diabetes mellitus (DM) and reducing diabetic vascular complications. They are considered protective factors. Deficiencies of both increase the risk of DM, and such deficiencies are the main reason for DM and its vascular complications. A summary of the positive effects of zinc and Vitamin C is presented in Fig. 11.

5.2. DM

DM is a metabolic disorder resulting from an imbalance and deficiency of certain elements that affect insulin hormone, which affects the metabolism of macronutrients (carbohydrates, lipids, and proteins) and some vitamins.

This affects the functions of the body, particularly the blood vessels, which leads to a decrease in blood flow or ischemia to many organs in the body, resulting in diabetic micro and macrovascular complications.

Zinc is the most significant element associated with DM. Diabetic patients are characterized by a deficiency of zinc. Zinc deficiency leads to:

1. Impaired pancreas function and secretion of the insulin hormone
2. Weakening of insulin function

Insulin is considered a glucose-, fat-, and protein-sparing hormone; insulin dysfunction leads to the following conditions:

A. High levels of blood glucose. In insulin resistance, glucose cannot enter the cells, which results in increased blood glucose levels. This forces the kidneys to excrete glucose through the urine, which causes polyuria.

B. High levels of blood lipids. In addition to insulin's inability to store lipids, the glucose cannot enter the cells. The cells, therefore, depend on lipids as an energy source, so the lipid level in the blood increases. As a result, lipid peroxidation increases, which causes a high oxidative stress state in the body.

C. High levels of breakdown protein products in the blood, such as urea and creatinine. Insulin dysfunction leads to an inability to store proteins effectively in the tissues, leading to the breakdown of proteins. Breakdown product levels in the blood increase, and they are excreted by the kidneys.

D. Vitamin C's inability to enter the cells, because it is dependent on insulin to enter the cells. In the case of insulin inefficiency or resistance, vitamin C cannot enter the cells. This leads to many problems, such as a decrease in nitric oxide (NO) bioavailability, which depends on vitamin C for its synthesis.

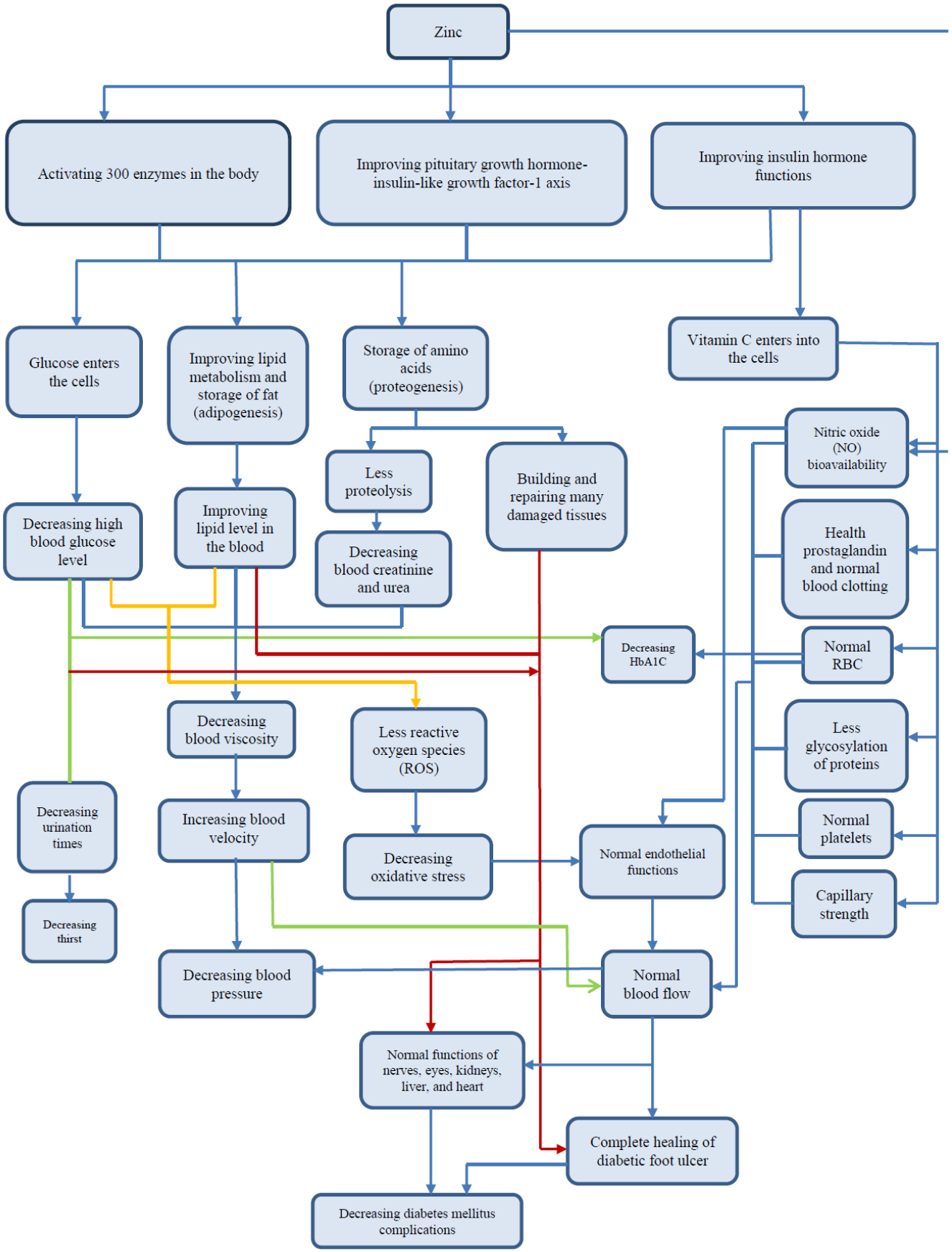

Fig. 11 Zinc and vitamin C effects on diabetes mellitus disease

Decreasing NO bioavailability is the result of vitamin C's inability to enter the cells, along with zinc deficiency, because zinc is a cofactor for vitamin C in the NO production process.

The oxidative stress state arising from lipid peroxidation increases the production of reactive oxygen species (ROS). ROS reduce the bioavailability of NO in the endothelium by reacting chemically with

NO to produce peroxynitrite (ONOO-). This leads to endothelial dysfunction, which leads to weakness in the blood capillary vessels, which are dependent on NO to function, finally resulting in impaired blood flow or ischemia.

Also, high glucose, lipids, and protein breakdown products levels in the blood increase the viscosity of the blood, which decreases the velocity of the blood flow, hence, ischemia.

High blood glucose levels and Vitamin C deficiency cause glycosylation of proteins, which leads to thickening in the basement membrane of capillaries, arterioles, and venules of blood vessels, which leads to less blood flow, hence ischemia.

So the impaired blood flow and ischemia in diabetes mellitus are resultant of three factors:

1. Decreasing nitric oxide (NO) bioavailability in endothelial tissues;
2. Increasing levels of glucose, lipids, and protein breakdown products in the blood;
3. Glycosylation of proteins

These factors lead to a decrease in blood flow to the vital organs in the body, which have high activity and need continuous blood flow, such as the eyes, kidneys, and nerves.

Therefore microvascular complications (retinopathy, nephropathy, and neuropathy) will appear in the first stages of the disease.

In the late stages of the disease, Macrovascular complications will appear, such as cardiovascular diseases (mostly coronary artery disease), cerebral vascular diseases, and peripheral vascular diseases because of vasa vasorum. These small blood vessels nourish the large blood vessels affected by the same mechanism of NO mentioned above.

Continuous impaired blood flow will result in ischemia, especially in peripheral blood vessels, which causes diabetic foot ulcers.

Due to impaired metabolism of macronutrients (carbohydrates, lipids, and proteins), which are associated and affect each other, diabetes mellitus is undoubtedly considered one of the fastest-growing non-communicable healthiness difficulties in the current century, known as a progressive disease.

In some cases of type 2 diabetes mellitus (long period diabetes mellitus), the disease turns to type 1 diabetes mellitus because of a lack of insulin secretion.

These cases are resultant from many factors, which are:

1. It affects the blood vessels (by the exact mechanism of NO mentioned above) that enter pancreatic β-cells. β-cells sense high blood glucose levels in these blood vessels and secrete insulin hormone. So high glucose level is considered a signal transporter to pancreatic β-cells to secrete insulin hormone and decrease blood glucose levels, reaching the normal level. Therefore, in this case, the blood does not enter the pancreas effectively, and the insulin hormone will not be secreted sufficiently or not.
2. Zinc deficiency impairs insulin hormone; hence glucose cannot enter the cells. Therefore the cells will use the lipids as an energy source instead of glucose, so more lipids peroxidation happens, generating more reactive oxygen species (ROS) that result in internal injury. Then apoptosis in pancreatic β-cells, as result, affects them, hence, the insulin hormone
3. Exhaustion of β-cells due to more insulin hormone secretion because of insulin resistance, which is considered a characteristic for type 2 diabetes.

So, the disease will develop into Type 1 Diabetes Mellitus, and the patient will depend on insulin hormone therapy. The developmental mechanism of diabetes mellitus disease is presented in Fig. 12.

5.3. Factors Affecting Response to Zinc and Vitamin C Administration

The factors which affect response to zinc and vitamin C administration are:

A. *Age:* The younger patients (30 and 40s) respond faster than older patients;

B. *Gender:* The men are faster in responding than women;

C. *Duration of disease:* New cases respond faster than older cases;

D. *Smoking:* Patients who smoke responded more slowly than non-smokers who responded quickly.

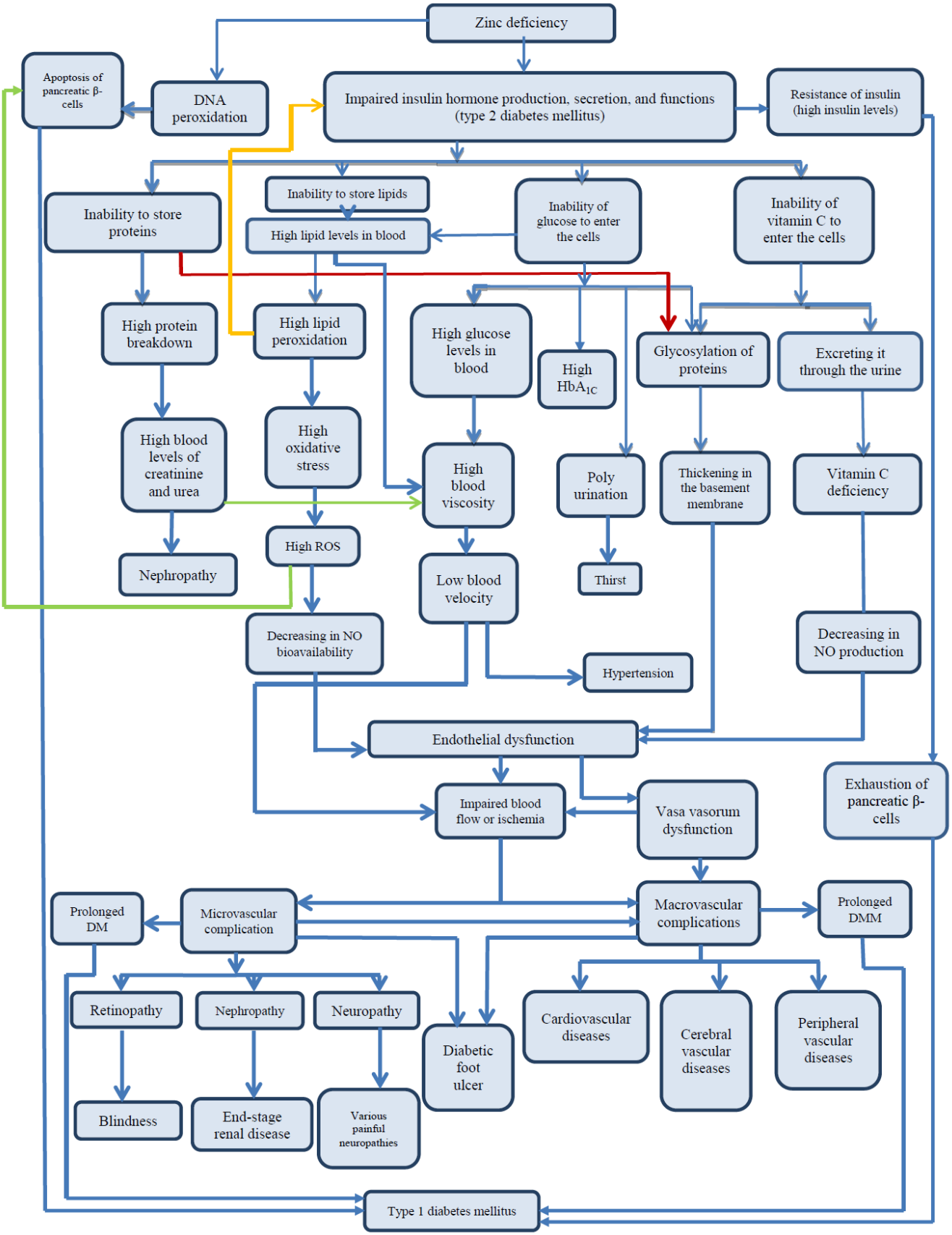

Fig. 12 Developmental mechanism of diabetes mellitus disease

5.7. Recommendations

1. For the severe diabetic cases with FBG of more than 300, the treatment doses could reach 150 or 200 mg for zinc and 1500 or 2000 mg for vitamin C. When the study was finished, zinc and vitamin C levels in the serum for those patients were with deficiency or insufficiency levels, especially vitamin C; or complete with 100 mg zinc and 1000 mg Vitamin C daily for a longer time.
2. According to the patients with a diabetic foot

ulcer, it is suggested to administrate vitamin C intravenously and double its dose to ensure it reaches the target sites.

3. The time for taking the supplements differs according to the different mealtime habits of different cultures. Because this study took place in Iraq, the times were specified according to the Iraqi routine which is characterized by a simple breakfast and the main meal at lunch. But these points must be considered:

A. To ensure its absorption, zinc must be taken after a simple meal that does not contain iron and copper, because these prevent zinc absorption.

B. Vitamin C must be taken about four hours or more after taking zinc because vitamin C aids iron absorption, which prevents zinc absorption. Zinc has a vital role in efficient insulin hormone production, ensuring entry of vitamin C to the cells, not excreting it through the urine. Therefore, the two doses must be separated when taken.

4. Monitoring of the blood glucose level during taking the supplements to avoid hypoglycemia, especially for patients undergoing insulin therapy or taking drugs that stimulate the pancreas to secrete insulin.

5. After the patient has taken and responded to these supplements (zinc and vitamin C) and reached the normal values for FBG, HbA1C, and insulin, it is recommended to preserve the supplement levels in the body through food sources or by administering supplements at recommended daily doses at the same times which are specified in this study.

6. People who have a hereditary predisposition for diabetes mellitus disease, and the probability of being affected at some point throughout their life, should periodically monitor zinc and vitamin C levels in their blood and improve decreasing levels with food sources or mentioned supplements at the times which are recommended in this study, to protect themselves from diabetes mellitus and its complications. All patients in this study suffered from an acute decrease in these supplements proportional to the disease-affecting period. The case with the highest duration of the disease is the most decreasing levels with these supplements.

7. If the patient finds it difficult to make breakfast simple, zinc can be taken an hour before breakfast.

8. It is recommended to give these supplements (zinc and vitamin C) to patients suffering from injuries, especially bone fractures, wounds, and burns. They should also be given to patients after medical surgery, due to the significant role – observed in this study – of the supplements in healing wounds. Wound healing was faster than that of a normal person without diabetes mellitus and not taking these supplements. In addition, the scars of the wounds disappeared, or they are barely seen. Taking them at the same times is recommended in this study.

9. It should not be adhered to the image of zinc in this study which is zinc oxide. It is possible to use another image, such as zinc citrate, which is better than zinc oxide, but was unavailable locally at the required dose.

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