Serum Glucose and Lipid Profile in Salt-Induced Metabolic Syndrome Rats Treated with Camel Milk

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Abstract: Metabolic syndrome is a complex disorder with high socioeconomic cost that is considered a worldwide epidemic. It is a group of interrelated risk factors of metabolic origin that directly promote the development of atherosclerotic cardiovascular disease (ASCVD). Camel milk is readily available, affordable and it is a good source of naturally occurring antioxidants. Therefore, the present study was carried out to investigate effect of camel milk supplementation on serum glucose and lipid profile in salt-induced metabolic syndrome rats. Rats were randomly divided into four groups: Group I: control animals (normal), Group II salts induced untreated, Group III: salt-induced supplemented with camel milk, Group IV salt-induced treated with 100mg/kg Metformin + 10mg/kg Nifedipine. Groups II, III and IV were placed on 8% salt diet for 6 weeks, which results in significant increase (P<0.05) in serum glucose, Total cholesterol (TC), Triglyceride (TAG), Low Density Lipoprotein Cholesterol (LDL-C), Very Low Density Lipoprotein-cholesterol (VLDL-C), and atherogenic index, and a significant decrease (P>0.05) in High Density Lipoprotein-cholesterol (HDL-C). Camel's milk supplementation counteracted the effect of high salts diet, reversed the above biochemical changes and improved them towards normalcy. This study suggests that regular consumption of camel milk could provide a natural way to protect against various component of metabolic syndrome.

Key words: Atherogenic Index, Camel Milk, lipid profile, metabolic syndrome, Salt-diet, Serum Glucose, Supplementation.

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Introduction

METABOLIC syndrome is a multiplex risk factor that arises from insulin resistance accompanying abnormal adipose tissue deposition and function [1]. It is a complex disorder associated with high socio-economic cost that is considered a worldwide epidemic and known to be a cluster of interconnected factors that directly increase the risk of coronary heart disease (CHD), various forms of cardiovascular atherosclerotic diseases (CVD) and type 2 diabetes mellitus (DMT2). Its main components are dyslipidaemia (elevated triglycerides (hypertriglyceridaemia) and apolipoprotein B (apoB)-containing lipoproteins and low high-density lipoproteins (HDL)). Elevation of arterial blood pressure (BP) and dysregulated glucose homeostasis, while abdominal obesity and insulin resistance (IR) have gained increasing attention as the core manifestations of the syndrome. Other abnormalities such as chronic proinflammatory and prothrombotic states, non-alcoholic fatty liver disease and sleep disturbances have been added to the entity of the syndrome [2]. Several cancers are reported among the clinical manifestations of the syndrome [3]. Apart from the above mentioned disorders, individuals with metabolic syndrome are prone to other adverse conditions notably, polycystic ovary syndrome, steatohepatitis and asthma [4].

Internationally, there is no uniformly accepted definition of metabolic syndrome [5]. However, it has been defined as a cluster of metabolic risk factors that come together in a single individual. According to Grundy *et al.* [6], Metabolic syndrome is diagnosed when a patient has at least 3 of the following 5 conditions:

a. Fasting glucose ≥100 mg/dL (or receiving drug therapy for hyperglycaemia)
b. Blood pressure ≥130/85 mm Hg (or receiving drug therapy for hypertension)
c. Triglycerides ≥150 mg/dL (or receiving drug therapy for hypertriglyceridaemia)
d. HDL-C < 40 mg/dL in men or < 50 mg/dL in women (or receiving drug therapy for reduced HDL-C)
e. Waist circumference ≥102 cm in men or ≥88 cm in women.

Several studies suggest that patients meeting these diagnostic criteria have a greater risk of significant clinical consequences, the two most prominent of which are the development of diabetes mellitus and coronary heart disease [7].

Approximately 1 adult in 4 or 5, depending on the country, shows features of the syndrome [8]. In the category of individuals over 50 years of age, it affects more than 40% of the population in the United States and nearly 30% in Europe [9]. In Nigeria, the estimated prevalence of metabolic syndrome was 16.8%, with a sex prevalence rates of 18.8 and 14.8% for males and females, respectively [10].

Several lines of evidence point to the role of increased oxidative stress in cardiovascular diseases (CVD). Oxidative stress and mainly superoxide anion ($^{\bullet}O_2^-$), plays a critical role in the pathogenesis of hypertension, hypertriglyceridaemia, diabetes, and obesity risk factors, defining metabolic syndrome [11]. In addition, it is thought to play a major role in the pathogenesis of atherosclerosis, aging, Alzheimer's disease, kidney disease and cancer [12]. In fact, available evidence suggests that metabolic syndrome is associated with elevated systemic oxidative stress [13]. Among other effects, an excess of $\bullet O_2^-$ may inactivate nitric oxide (NO), thus leading to endothelial dysfunction which in turn, facilitates vascular abnormalities [14]. Furthermore, an increased production of $^{\bullet}O_2^-$ may facilitate oxidative modification of proteins [11], by rendering nitrotyrosine which constitutes a strong and independent predictor of cardiovascular disease [15]. $^{\bullet}O_2^-$ is also involved in LDL oxidation, a key step in the initiation and progression of atherosclerosis [16]. ox-LDL is not recognized by the LDL receptor, can be taken up by scavenger receptors in macrophages leading to foam cell formation and atherosclerotic plaques [17].

Milk plays a significant role in human's nutrition for the wonderful reason that they are excellent sources of various nutrients. Camel milk has been suggested in the management of various diseases [18]. Camel milk has medicinal properties including antibacterial and antiviral activity [19], which may be due to higher concentration of lactoferrin, immunoglobulins, lysozyme and vitamin C [20]. Badriah, [21] reported that camel milk is effective in the treatment of diabetes, which may be due to its insulin like activity, regulatory and immuno modulators effects on beta cells.

It was earlier reported that Camel milk is characterized with low cholesterol, low sugar, high minerals (sodium, potassium, iron, copper, zinc and magnesium), high vitamins (A, B2, C and E) and large concentrations of insulin [22]. These vitamins act as antioxidants and have been found to be useful in preventing toxicant-induced tissue injury [23].

Camel milk is readily available and affordable in many Nigerian communities and several studies demonstrated the high potential therapeutic properties of Camel milk. These qualities trigger our curiosity and choice of the milk supplementation to investigate whether it could be useful in the management of experimentally induced metabolic syndrome.

Materials and Methods

Chemicals and Reagents

Analytical grade laboratory chemicals and reagents were used for this study.

Glucose oxidase Kit, Total Cholesterol assay kit, Triglyceride assay kit and HDL-C assay kit, Superoxide dismutase assay kit (product of Randox), were used in this work.

Experimental Animals

Westar albino rats of both sexes weighing between 150-220g were used for the study. The animals were purchased and allowed to acclimatize for 7 days before the commencement of the experiment. All animals were housed in cages (8 rats/ cage), and fed with pelletized growers' feed (Vital feed, Jos, Nigeria) and allowed access to water *ad libitum* before and during the experimental period.

Induction of Metabolic Syndrome in Rats

The rats were placed on 8% w/w salt diet [24] except the control group, for 6 weeks and treatment with Camel milk for additional 4 weeks.

Measurement of Blood Pressure

The baseline blood pressure was measured by tail-cuff method using non-invasive Ugo Basile, series 58500 blood pressure recorder. The average of three readings was taken for each rat and the weekly systolic and diastolic blood pressure of the rats were monitored throughout the experimental period.

Collection of Milk Sample;

The milk was collected by cameleer using hand milking from lactating camel (*Camelus dromedarius)*, near Usmanu Danfodiyo University Second Gate at Kwalkwalawa Village, Wammakko Local Gov't area of Sokoto State, Nigeria. It was collected in a sterile screw jar and kept in a cool container with ice block until transported to the laboratory where it was kept at temperature of -4^{0}C. The pH of the milk was checked every day before administration, to monitor the freshness of the milk.

Grouping of Animals*:*

The animals were randomly divided into 4 groups of 8 rats each, and orally treated as follows:

Group I: normal, control group

Group II: salt-loaded, untreated.

Group III: salt-loaded treated with Camel milk (5mls/kg b.w/day).

Group IV: salt-loaded, orally dosed with 100mg/kg Metformin + 10mg/kg Nifedipine.

Preparation of Serum

Twenty four hours after the last treatment, the animals were anaesthetised with chloroform vapour and blood samples were collected through cardiac puncture into labelled tubes for biochemical analyses. Prior to this, the animals were subjected to overnight fasting. The blood samples collected were allowed to clot and centrifuged at 4000g for ten minutes. The sera obtained were pipetted into labeled test tubes for estimation of serum glucose and lipid profiles.

Biochemical Analyses

Serum glucose was estimated by glucose oxidase method using Randox kit [25]. Serum total cholesterol (TC) was estimated by enzymatic method using Randox kit [26].

Serum HDL- C was estimated by enzymatic method of Burstein *et al.,* [27] using Randox Kit. Serum Triglyceride was assayed by the method of Tietz [28], using Randox Kit.

Serum LDL- C was calculated using Friedewald formula [29].

$$LDL\text{-}C(mg/dl) = TC - (HDL\text{-}C) - \left(\frac{TG}{5}\right)$$

Serum VLDL- C was calculated using Friedewald formula [29].

$$VLDL\text{-}C\ (mg/dl) = \frac{TG}{5}$$

Atherogenic Index (AI) was calculated as the ratio of LDL-cholesterol to HDL-cholesterol according to Abbott *et al.* [30].

% Protection against Atherogenesis was calculated using the following equation:

$$\%Protection = \frac{AI\ of\ control - AI\ of\ treated\ group}{AI\ of\ control} \times 100$$

Statistical Analysis.

Data were expressed as mean ± standard deviation of 8 rats in each group. All the biochemical parameters were analysed statistically using Student's t-test where two variables are compared and one way analysis of variance (ANOVA) for more than two variables, using Graph pad instat software (version 5 San Diego, U.S.A). Results were considered statistically significant at p<0.05.

Results

Effect of high salt-diet on Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) before and after administration are presented in table 1: the results indicate that administration of high salts diet (8% w/w) to rats for 6 weeks significantly increased (P>0.05) the SBP as compared with control group. On the other hand, no much variation was observed on DBP between salt-administered groups and control group.

Table 1: Systolic and Diastolic blood pressure before and after 8% salt diet administration

	Before		After	
Groups	SBP(mmHg)	DBP(mmHg)	SBP(mmHg)	DBP(mmHg)
I	$122.23^{a}\pm1.45$	80.55±2.87	$120.45^{a}\pm1.23$	78.65±1.33
II	$121.90^{a}\pm2.89$	79.82±2.65	$147.88^{b}\pm0.91$	89.24±1.86

LEGEND: Group I: control and Group II: salt-loaded. Values are expressed as mean ± S.D of eight replicates. Mean values having different superscript letters in rows are significantly different (p<0.05) SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

The results of the effect of 8% w/w salt-diet on serum glucose, lipid profile and atherogenic index of salt loaded rats before treatment was presented in Table 2 The result indicates significant increase (P<0.05) in the levels of serum glucose, total cholesterol, triglyceride, LDL-C, VLDL-C and atherogenic index of the salt treated groups as compared with control group, while HDL-C decreased significantly (P<0.05) in salts- loaded groups in comparison with control group.

Table 2: Serum glucose lipid profile and atherogenic indices of salt-loaded rats before treatment.

Parameters (mg/dl)	Groups I	II
[Glc]	85.14 ± 1.45^{a}	129.60 ± 0.55
[TC]	95.62 ± 5.94^{a}	163 67 ±5 .51
[TAG]	93.63 ± 6.55^{a}	163.33 ± 2.52
[HDL-C]	34.67 ± 5.13^{a}	23.67 ± 2.51
[LDL-C]	42.21 ± 3.25^{a}	109.67 ± 2.87
[VLDL-C]	18.72 ± 1.32^{a}	32.67 ± 0.50
AI	1.24 ± 0.25^{a}	4.67 ± 0.56

LEGEND: Glc- glucose, TC- total cholesterol, TG- triglyceride, HDL-C- high density lipoprotein cholesterol, LDL-C- low density lipoprotein-cholesterol, VLDL-C- very low density lipoprotein-cholesterol, AI: atherogenic index. Group I: control and Group II: salt-loaded. Values are expressed as mean ± S.D of four replicates. Mean value having different superscript letters in rows are significantly different (p<0.05)

The results of the effect of Camel milk supplementation on serum glucose lipid profile and atherogenic indices in salt-induced metabolic syndrome rats after two weeks of treatment is presented in Table 2. The result indicated statistically significant decreased (P<0.05) in the levels of serum glucose, VLDL-C and AI of the Camel milk supplemented groups after two weeks of treatment as compared with salt-loaded untreated group. With the exception of TAG and HDL, no statistical significant (P>0.05) difference was observed between group supplemented with Camel milk and control group. The results also indicates statistically significant decrease (P<0.05) in serum glucose TC, TAG and LDL in a group dosed with 100mg/kg Metformin + 10mg/kg Nifedipine in comparison with salt-loaded untreated group.

Table 3: Serum glucose, lipid profile and atherogenic indices of salt-induced metabolic syndrome rat's after two weeks of treatment.

Parameters (mg/dl)	Groups I	II	III	IV
[Glc]	97.56 ± 0.31^{a}	149.58±0.43	114.66 ± 0.26^{ab}	88.38 ± 0.35^{a}
[TC]	91.00 ± 3.00^{a}	143.00 ± 6.06^{b}	112.67 ± 8.51^{ab}	94.33 ± 7.10^{a}
[TAG]	92.66 ± 11.05^{a}	154.67 ± 3.58^{b}	131.00 ± 5.69^{bc}	88.33 ± 5.78^{a}
[HDL-C]	44.33 ± 4.09^{a}	30.33 ± 3.06^{b}	31.00 ± 5.00^{bc}	41.67 ± 3.06^{abc}
[LDL-C]	28.13 ± 4.51^{a}	81.73 ± 6.47^{b}	55.47 ± 4.36^{abc}	35.00 ± 4.12^{ac}
[VLDL-C]	18.53 ± 2.20^{a}	30.93 ± 2.72^{b}	17.66 ± 2.00^{a}	26.20 ± 1.97^{b}
AI	0.66 ± 0.28^{a}	2.77 ± 0.20^{b}	0.85 ± 0.28^{ac}	1.83 ± 0.49^{abc}

LEGEND: Glc- glucose, TC- total cholesterol, TG- triglyceride, HDL-C- high density lipoprotein- cholesterol, LDL-C- low density lipoprotein-cholesterol, VLDL-C- very low density lipoprotein- cholesterol, AI- atherogenic index. Group I: control, Group II: salt-loaded untreated, group III: salt-loaded treated with Camel milk (5mls/kg b.w/day) Group IV: salt-loaded orally dosed with 100mg/kg Metformin + 10mg/kg Nifedipine. values are expressed as Mean ± S.D of four replicates. Mean values having different superscript letters in rows are significantly different (p<0.05)

The results of the serum glucose lipid profile and atherogenic indices of salt-induced metabolic syndrome rats after four weeks of treatment are presented in Table 3. Statistical analysis of the results revealed significant decrease (P<0.01) in serum glucose of the camel milk supplemented group as compared with salt-loaded untreated group. There was no statistical significant difference (P>0.05) between supplemented groups and control. Significant (P<0.01)

increase in serum glucose levels occurred in salt-loaded untreated groups as compared with control. Significant decrease (P<0.001) was observed in TC, TAG, LDL-C, VLDL-C and AI of the group supplemented with Camel milk compared to salt-induced untreated group. On the other hand, serum level of HDL-C of Camel milk supplemented group increased significantly (P<0.01) when compared with salt-induced untreated group. The results also showed strong similarities (P>0.05) in TC, TAG, HDL-C, LDL-C, VLDL-C and AI between the group supplemented with camel and control group, so also no statistical significant different (P>0.05) is observed between the group supplemented with Camel milk and the group treated with 100mg/kg Metformin + 10mg/kg Nifedipine.

Table 4: Lipid profiles and atherogenic indices of salts- induced metabolic syndrome rats, after four weeks of treatment

Parameters (mg/dl)	Groups			
	I	II	III	IV
Gluc	91.80±2.76[a]	160.20±.1.30[b]	75.96±2.80[ac]	82.26±0.64[ac]
TC	95.33±6.03[a]	178.33±6.02[b]	92.00±5.03[ac]	101.67±6.88[ac]
TAG	101.67±9.20[a]	172.33±6.77[b]	100.33±5.89[ac]	111.33±8.45[ac]
HDL-C	47.67±5.51[a]	27.33±5.86[b]	53.67±7.42[ac]	56.33±3.51[ac]
LDL-C	27.33±2.72[a]	116.50±7.80[b]	18.27±5.92[ac]	23.07±4.60[ac]
VLDL-C	20.33±3.19[a]	34.50±2.36[b]	20.07±2.04[ac]	22.27±2.93[ac]
AI	0.58±0.11[a]	4.450±0.14[b]	0.36±0.20[ac]	0.41±0.13[ac]

LEGEND: Gluc- glucose TC- total cholesterol, TG- triglyceride, HDL-C- high density lipoprotein- cholesterol, LDL-C- low density lipoprotein-cholesterol, VLDL-C- very low density lipoprotein- cholesterol, AI- atherogenic index. Group I; control, Group II: salt-loaded untreated, group III: salt-loaded treated with Camel milk (5mls/kg b.w/day) Group IV: salt-loaded orally dosed with 100mg/kg Metformin + 10mg/kg Nifedipine. Values are expressed as mean ± S.D of eight replicates. Mean value having different superscript letters in rows are significantly different (p<0.05)

The result of mean percentage protection against atherogenesis of salt-induced metabolic syndrome rats supplemented with camel milk is presented in Figure 1. The result indicated 91.93% percentage protection in the group supplemented with Camel milk, while the group treated with 100mg/kg Metformin + 10mg/kg Nifedipine observed to have (90.9%) %protection against atherogenesis. Control group showd the lowest %protection of 86.6.

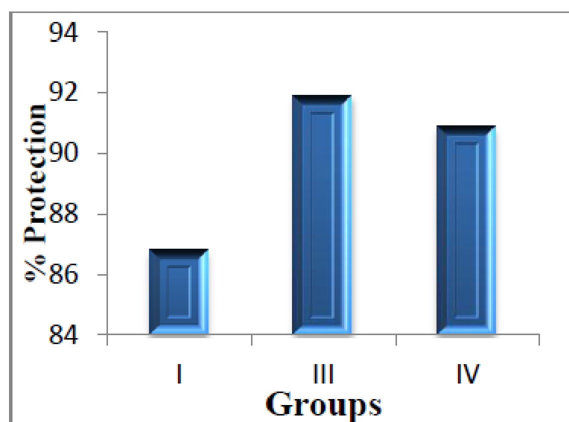

Figure 1: Mean percentage protection against atherogenesis of salt-loaded rats supplemented with Camel milk.

Discussion

Metabolic syndrome is a complex disorder with high socioeconomic cost that is considered a worldwide epidemic. Epidemiological studies and clinical trials suggested that diets, characterized with significant amount of naturally occurring antioxidants appear to relif most of the traits of metabolic syndrome and may reduce risk of cardiovascular diseases [31]. In this study, 8% salt-diet was used to induce metabolic syndrome in Wistar albino rats for a period of 6 weeks. This is due to the fact that, a high-salt diet, which is known to contribute to the pathogenesis of hypertension, was also reportedly associated with insulin resistance, which eventually led to the development of insulin resistance syndrome otherwise called metabolic syndrome [32]. Toshiro [33] also suggested that salt-induced insulin resistance might be attributable to the overproduction of ROS, which is one of the key factors in the pathogenesis of many component of metabolic syndrome.

Our findings indicated that, in addition to increase in blood pressure, salt-loaded rats had elevated levels of plasma total cholesterol (TC), triglycerides (TG), low density lipoprotein-C (LDL-C), very low density lipoprotein-C (LDL-C), and decreased (P<0.001) level of high density lipoprotein-C (HDL-C) as well as atherogenic index (AI). These parameters were known to be the hall-marks of metabolic syndrome .Treatment with Camel milk prevented the above mentioned changes and improved them towards normal levels in the experimental rats. The mechanism of high salt diet-induced metabolic syndrome could be attributed to increase concentration of sodium in circulation which in turn activates sympathetic nervous system and renin-angiotensin-aldesterol-system (RAAS). [34] as well as increased signaling through the mineralocorticoid receptors (MR) [35]. These may lead to increase production of reactive oxygen species which result to oxidative stress, and finally contribute to aetiopathology of insulin resistance, high blood pressure, impaired glucose homeostasis and dyslipidaemia [36]. Other possible mechanism is that, high salt diet is associated with the activation of adipokines (leptin, angiotensinogen, tumour necrosis factor α, transforming growth factor β and resistin,) that may stimulate hepatic TAG synthesis, which in turne promote the assembly and secretion of LDL, VLDL and reduction of HDL cholesterols [37]. Obesity, insulin resistance, and diabetes may also be induced [38]. This hyperlipidemia could be related to the enhanced de-esterification of the abundant FFAs and decreased lipoproteins. This finding confirmed the reports that salt loading to various strains of rats such as Sprague-Dawley rats [39], Wistar rats [40] and Dahl salt-sensitive rats [41] could result to increased mean arterial blood pressure, inhibition of insulin signalling and induces insulin resistance.

Camel milk is reportedly an excellent source of components that are involved in some biological activities, one of which is defence against free radicals and reactive oxygen species [42]. Therefore, it can suppress the effects of the reactive oxygen species in order to delay the onset and progress of metabolic syndrome. This may be the reason for its potentials in normalizing the above changes observed in salt-induced metabolic syndrome rats.

Several studies have indicated a strong relationship between hypertension, dyslipidaemia, insulin resistance and hyperglycaemia [43], which are consequences of over production of reactive oxygen species. This study found a statistically significant (P<0.05) decrease in serum Glu, TC, TAG, LDL-C, VLDL-C and AI, and significant (P<0.01) increase in HDL-C of all the rats supplemented with Camel milk, compared with non-supplemented rats. The obvious amelioration of the hyperlipidemia and dyslipidaemia in the Camel milk supplemented group is in agreement with recent reports about fresh and fermented Camel milk containing

Bifidobacteria, which lower plasma lipids in rats administered with a high-cholesterol diet [44], [45]. The hypolipidemic effect of Camel milk could be due to its high content of L-carnitine, which decreases cholesterol absorption [46], [47]. In addition, two indirect mechanisms could also be proposed for the ability of camel milk in the improvement of the lipid profile: Camel milk may exert local effects on the stomach to inhibit gastric emptying or decrease food intake through stimulation of sense of satiety. Camel milk may affect the PPAR alpha/SREBP1 ratio, as stated in the work conducted by Ziamajidi , *et al.,* [48],which led to increase the activity of the fat-metabolizing enzymes and hormones, this results in increased caloric loss and decreased fat storage. These mechanisms could influence insulin sensitivity in order to improve glucose homeostasis. Our finding is consistent with the work of Korish and Arafah, [49]. The reduced HDL level found in non supplemented group has several reasons one of which is increased concentrations of plasma VLDL drive the exchange of triglycerides from VLDL for the cholesteryl esters found in HDL [50]. Moreover, the triacylglycerol in HDL is a substrate for plasma lipases, especially hepatic lipase that converts HDL to smaller particle that is more rapidly cleared from the plasma. Additionally, Goldberg [51] observed that a defective lipolysis leads to reduced HDL production. Therefore, the VLDL and TG lowering effect of Camel milk through the above possible mechanism might be responsible for the increased serum concentration of HDL in Camel milk supplemented group. Earlier studies suggested that the improvement in lipoproteins was due to the effect of vitamin C and Zinc in the Camel milk, which are potential antioxidants [52].

High salt diet initiates the production of reactive oxygen species (ROS) that can oxidize LDL cholesterol leading to atherogenesis [53]. Highest average percentage protection (91.93%) against atherosclerosis was observed in the Camel milk supplemented group. This could be attributed to the high content of antioxidant in the Camel milk responsible in chain breaking thereby donating hydrogen atoms to free radicals in order to protect the cells from lipid peroxidation [54], [55].

Conclusion:

The findings of this study led us to conclude that the Biochemical abnormalities induced by High-salt diet, including hyperlipidaemia, hyperglycaemia and hypertension were markedly restored to near normal levels by camel milk treatment. These findings support the reported health-promoting effects of Camel milk. Hence, it can be used as a therapeutic adjuvant in metabolic syndrome and its associated complications resulting from unhealthy lifestyles and eating habits.

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