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Fluctuation of Serum Apelin Level during Pregnancy

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Authors' contributions

This work was carried out in collaboration among all authors. Author SWM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AKA, KIA and SEISM managed the analyses of the study. Author AD managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Apelin is an endogenous ligand for the G protein-coupled receptor Apelin receptor (APJ), The expression of both apelin and APJ has been detected in a variety of tissues including heart, brain ,ovary , placenta and uterus.
Aim of the Study: This study was designed to examine the circulating levels of apelin, estradiol, progesterone, glucose, insulin and Tumor necrosis Factor alpha (TNF α) in non-pregnant, pregnant rats at different stages of pregnancy.
Materials and Methods: Sixty adult albino rats (48 females and 12 males). Female rats were randomly divided into (non -pregnant rats, early pregnant rats on day 6 of gestation, mid pregnant rats on day 12 of gestation and rats late pregnant rats on day 19 of gestation. The blood samples were obtained from the orbital venous plexus of animals and serum was separated from each blood sample and kept deep frozen until analysed.
Results: The present study revealed that the serum levels of apelin were progressively and significantly increased from early (day 6) to mid-pregnancy (day 12) of gestation when compared to non- pregnant rats then showed a marked decrease on day 19 when compared to pregnant rats on day 12 of gestation.

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Conclusion: The fluctuations in serum apelin levels during pregnancy may be attributed to changes in serum levels of multiple interrelated factors such as insulin, insulin resistance, pro inflammatory cytokines such as TNF α and other factors such as changes in fat mass, the expression of angiotensin converting enzyme related carboxy peptidase-2 (ACE 2) and hormonal levels during pregnancy.

Keywords: Apelin; placenta; pregnancy.

1. INTRODUCTION

Apelin is an adipokine and the endogenous ligand for APJ, an angiotensin-1-like receptor. It had been isolated from the bovine stomach [1]. Before the isolation of apelin, the APJ receptor was referred to as an orphaned G-protein-coupled receptor (GPCR) because its endogenous ligand was unidentified [2].

Apelin and APJ were detected in various tissues and organs such as stomach, brain, heart, lung, uterus, ovary and produced in pregnant and lactating breast, high levels were identified in the placenta suggesting a possible placental origin of apelin in pregnancy [3].

Mayeur et al. [4] found that human maternal plasma apelin levels were increased significantly and progressively during pregnancy reaching a peak level at day 17 despite they observed a significant decrease in plasma apelin levels during the 1st few days of pregnancy. Also, Josephs et al. [5] demonstrated that apelin mRNA in human white adipose tissue was increased 2.2-fold at day 7 of pregnancy that may be attributed to fat accumulation. Moreover, Mieghem et al. [6] showed that maternal plasma apelin levels were decreased in the last week of rat gestation likely due to increased elimination by the feto placental unit.

In contrast, Kacar et al. [7] found that apelin concentrations were significantly high at late pregnancy but significantly low in first few days following labor. Also, serum apelin levels have been shown to be decreased in the second trimester of pregnancy compared with non-pregnant controls; however, fetal levels have been shown to be markedly increased on day 1 and day 4 of life [8].

Because of these contradictory reports, the present study was designed to Examine the circulating levels of apelin, estradiol, progesterone, glucose, insulin and TNF α in non-pregnant, pregnant rats at different stages of pregnancy.

2. MATERIALS AND METHODS

Sixty healthy adult albino rats (48 female rats and 12 male rats) were obtained from the laboratory animals' farm unit Faculty of Veterinary Medicine, Zagazig University, with an average weight, 180-200 grams. The animals were kept in steel wire cages (6/cage) under hygienic conditions and kept on the diet which consisted of mixed commercial rat laboratory chow and supplied in separate clean containers. Animals had free access to water and kept at room temperature. All animals were bred in the animal house. The rats were accommodated to laboratory conditions for two weeks before the starting of the experiments. The male rats were used for induction of pregnancy.

The animals were randomly divided into the following four groups (12 for each):

Sixty adult albino rats (48 females and 12 males). Female rats were randomly divided into four groups, 12 in each one (non -pregnant rats , early pregnant rats on day 6 of gestation , mid pregnant rats on day 12 of gestation and rats late pregnant rats on day 19 of gestation).

2.1 Methods

2.1.1 Determination of sexual cycle

Smears were obtained daily by vaginal washing using saline and fresh unstained samples were analysed microscopically , cycles with duration of 4 to 5 days were considered regular [9]. The four phases of the estrus cycle were assessed according to analysis of vaginal cytology according to Goldman et al. [10].

2.1.2 Determination of the first day of pregnancy

Vaginal smears taken from the female rats were examined daily by using light microscope to ensure that they were in regular estrus cycle. The estrus phase of the estrus cycle was detected by the presence of cornified epithelial

cells which increase in number and eventually predominate as the estrus progresses [11].

The female proved to be in estrus phase was paired with a mature male rat in a separate cage. After mating, females were subsequently isolated until the time of analysis to ensure accurate gestation timing, and in the next morning a vaginal smear taken. Copulation was confirmed by the presence of a copulation plug or spermatozoa in the vagina. The presence of sperms indicated the first day of pregnancy [12]. Parturition usually occurs in the evening of day 21 or the morning of day 22 as the duration of pregnancy in rats is about 21 days [13].

Blood samples were obtained from orbital venous plexus of animals, these samples were allowed to clot for 2 hours at room temperature before centrifuging for 15 minutes at approximately 3000 rpm [14].

The separated serum was stored at -20°C. Repeated freezing and thawing were avoided [15] until assayed for apelin, estradiol, progesterone, prolactin, TNF-α, in addition to insulin and glucose levels.

Estimation of serum apelin levels, according to the methods of Porstmann and Kiessig, [16] using Rat Apelin ELISA kits: (Sun Red, Biotechnology, shanghai).Estimation of serum estradiol and progesterone levels according Tietz, [17] using rat kits BC-1111 and BC-1113 Bio Check, Inc 323 Vintage Park Dr. Foster City, CA 94404 respectively, Bio Chepck, Inc. 323 Vintage Park Dr. Foster City, CA 94404).

Estimation of serum glucose level according to Tietz [17] and serum insulin level by enzyme–linked immunosorbent assay (ELISA) according to Temple et al. [18]. Kits for estimation of serum glucose and insulin levels were purchased from (Biosource Europe S.A.Belgium). Measurement of homeostasis model assessment (HOMA-IR) index was calculated according to Sun et al. [19] as follows: [HOMA-IR] = fasting serum glucose (mg/dl) × fasting serum insulin (μIU/ml)/405.

Estimation of serum of TNF-α *using TNF-α Immunoassay Kits, (Rat), Catalog Number KRC3011*.

2.3 Statistical Analysis

Data were presented as mean ± SD. Statistical significance was determined by one-way ANOVA between groups and correlation coefficient (r). $P<0.05$ was considered statistically significant. SPSS version (14) program for Windows (SPSS Inc. Chicago, IL, USA) was used.

3. RESULTS

The present study shows a high apelin plasma level during pregnancy in comparison with control non- gravid rats, the highest was in mid - pregnant group (12 days of gestation) $p<0.001$ (Table 1).

A strong positive correlation was detected between HOMA-IR and serum apelin levels (pg/ml) in group 2a (day 6 of pregnancy) group 2b (day 12 of pregnancy) $p<0.001$. However a significant negative correlation was found between HOMA-IR and serum apelin levels (pg/ml) in group 2 c $p<0.01$ Fig 1.

A strong positive correlation was detected between serum levels of TNF-alpha (pg/ml) and serum apelin levels (pg/ml) in group 2a (day 6 of pregnancy) group 2b (day 12 of pregnancy) $p<0.001$. However a strong negative correlation was found between serum levels of TNF-alpha (pg/ml) and serum apelin levels (pg/ml) in group 2 c $p<0.001$ Fig 2.

A strong positive correlation was detected between HOMA-IR and TNF-alpha in three pregnant groups 2a (day 6 of pregnancy) group 2b (day 12 of pregnancy) and group 2c (day 19 of pregnancy) Fig. 3.

Table 1. The mean values ± SD of serum levels of all studied parameters

N = 12	Group 1 non pregnant	Group 2a early pregnant (day 6)	Group 2b mid-pregnant (day 12)	Group 2c late pregnant (day 9)
Apelin (pg/ml)	291.25 ± 52.28	528.25 ± 59.48	781.08 ± 48.33	498.50 ± 64.93
Estradiol (pg/ml)	9.93 ± 1.44	17.69 ± 2.44	23.22±2.715	30.27±2.83
Progesteron (ng/ml)	13.77 ± 2.59	45.21 ± 3.99	66.73±3.98	73.50±4.92
Insulin (μIU/ml)	7.19 ± 1.94	10.90 ± 1.13	17.18 ± 2.64	18.77 ± 2.63
Glucose (mg/dl)	83.08 ± 7.15	88.42 ± 7.46	83.58 ± 7.16	89.83 ± 8.68
HOMA-IR	1.37 ± 0.46	2.36 ± 0.19	3.55 ± 0.67	4.16 ± 0.70
TNF α (pg/ml)	1.76 ± 0.14	1.96 ± 0.13	2.37 ± 0.28	2.60 ± 0.26

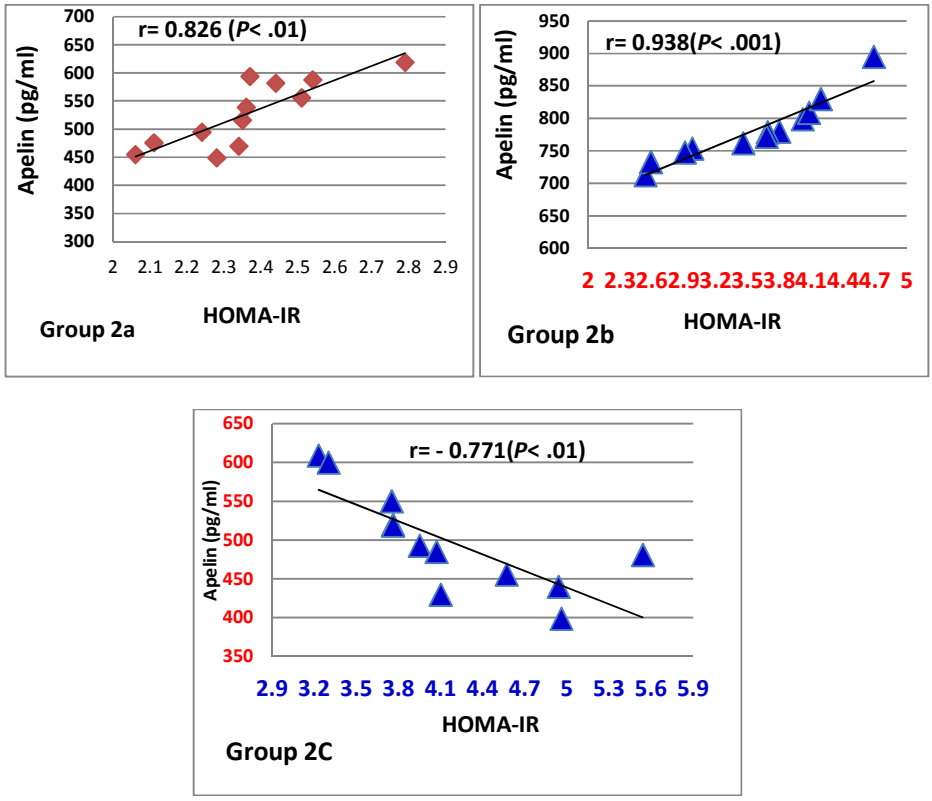

Fig. 1. Correlation between apelin and HOMA-IR in different studied groups

Correlation between serum levels of TNF-alpha (pg/ml) and serum apelin levels (pg/ml) in group 2a (day 6 of pregnancy) group 2b (day 12 of pregnancy) and group 2c (day 19 of pregnancy)

4. DISCUSSION

The present study revealed that serum apelin levels in rats were significantly increased in early (day 6) and mid- pregnancy (day12) when compared to non-pregnant. However, there was a significant decrease in late pregnancy (day19) when compared with mid pregnancy.

The results of the present study were in accordance with those of Mayeur et al. [4] who found that maternal plasma apelin levels were increased significantly and progressively during gestation period reaching a peak value at day 17 accompanied with a significant decrease in plasma apelin levels during the first few days of pregnancy and at term. They attributed the reduction in apelin plasma level at term to an increase in apelin clearance by the placental (ACE2) angiotensin converting enzyme related carboxy peptidase-2. However, the findings of the present study were at variance with those of Kourtis et al. [8] who observed that serum apelin levels were significantly lower in pregnant females (2nd trimester) than non-pregnant ones.

Also, Medhurst et al. [20] showed that the pre pro apelin mRNA is ubiquitous in human tissues with increased levels in the placenta which suggest a potential placental production of apelin during pregnancy. Moreover, Telejko et al. [21] reported that apelin mRNA expression was approximately 10 folds higher in the placenta than in adipose tissue of pregnant woman.The changes or the fluctuations in serum apelin levels, observed in the present study, during pregnancy could be explained by the following possibilities.

The 1st possible explanation is the change in angiotensin converting enzyme related carboxy peptidase-2 (ACE2) which was considered by Kalea and Batlle [22] as the only enzyme known to hydrolyze apelin. However, Mckinnie et al. [23] reported that the metalloprotease neprilysin (NEP) is an another enzyme that can cleave apelin isoforms .*Van* Mieghem et al. [6] found

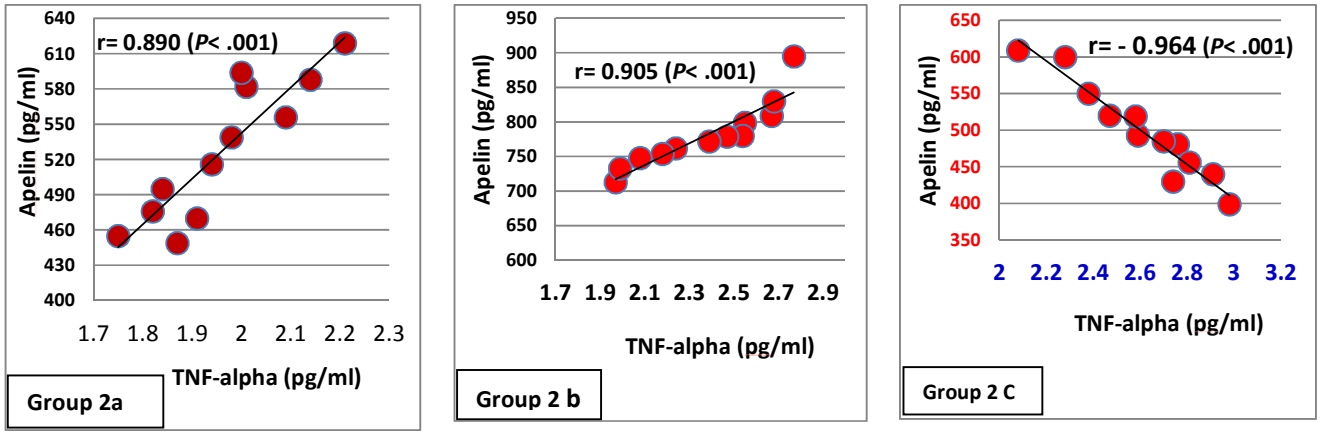

Fig. 2. Correlation between TNF-alpha (pg/ml) and serum apelin levels in different studied groups

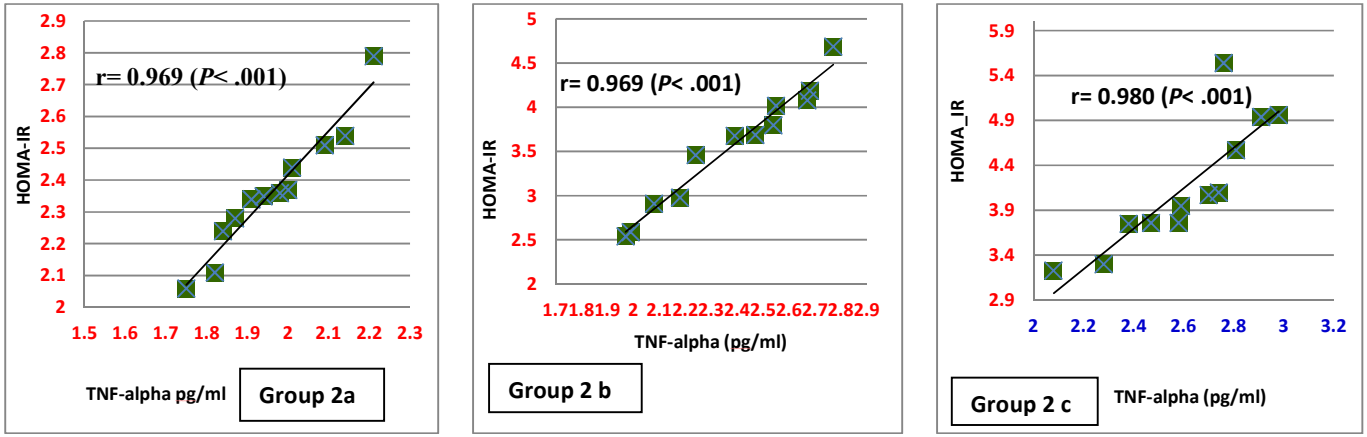

Fig. 3. Correlation between calculated values of HOMA-IR and serum levels of TNF-alpha (pg/ml) indifferent studied groups

that the expression of ACE2 mRNA was detected in late- but not mid-pregnancy placental tissue explaining the drop in maternal apelin levels by~ 50% considerably between mid and late normal rat gestation. They postulated that the reduction in apelin levels late in pregnancy was not due to decreased tissue production but was most probably due to increased elimination of apelin by the feto placental unit.

The 2nd possible explanation for the changes in apelin levels during pregnancy may be due to changes in insulin sensitivity and resistance during pregnancy.

Boucher et al. [24] observed that apelin and APJ were expressed in adipocytes. Also, they reported that apelin secretion and expression is regulated by insulin through stimulation of phosphatidylinositol 3-kinase, protein kinase C, and mitogen activated protein kinase.

Peripheral insulin sensitivity remains stable or slightly increased in the first trimester, providing optimal conditions for glucose and lipid uptake [25], In the second trimester, peripheral insulin response decreases and postprandial hyperglycemia becomes apparent Furthermore, fasting glucose production in the liver increases, a sign of impaired hepatic insulin sensitivity. In late pregnancy, total body insulin sensitivity is reduced, insulin secretion is twice as high as in the non-pregnant state with an increase in pancreatic β-cell mass, and basal glucose levels are reduced despite increased hepatic glucose production [26].

Kourtis et al. [8] compared pregnant women (24th–28th week of gestation) with non-pregnant controls in terms of insulin sensitivity, lipid levels, oxidative stress and serum apelin levels. They found higher serum levels of insulin and lower serum levels of glucose in the pregnant group indicating that pregnancy is a state of mild insulin resistance This is in accordance with other studies [27].

In addition, Kourtis et al. [8] found that serum levels of apelin were significantly lower in pregnant (which is characterized by a state of mild insulin resistance) than in non-pregnant. Previously published studies showed significantly lower levels of apelin in cases of type II diabetes compared to healthy controls [28] .In contrast, other studies have reported increased levels of apelin in type II diabetes [29]. On the other hand, it has been suggested that in obesity either associated with type II diabetes or not, apelin is up regulated in both mice and human [24].

There are several factors which contribute to the development of insulin resistance. The first are the placental hormones, most of which are secreted in continually increasing quantities as the pregnancy progresses. Initially, human placental lactogen, progesterone, estrogen, and placental growth hormone were believed to be the main causes of insulin resistance. However, the current opinion is the adipokines such as TNF-α, leptin, and adiponectin play a more significant role [30]. There present study revealed that there was a significant positive correlation between insulin resistance HOMA IR and TNF α.

García-Arencibia et al. [31] have shown that estradiol reduces insulin receptor gene expression and glucose transport, involving the estrogens in the induction of insulin resistance in the latter part of pregnancy but the contribution of estradiol to the development of insulin resistance is relatively minor compared to that of several other pregnancy hormones.

Also, The rise in progesterone is proportional to the decrease in insulin sensitivity observed during the second half of pregnancy, pointing to a role for progesterone in this process. In late gestation, when levels are highest, progesterone contributes to insulin resistance by reducing insulin binding, glucose transport, and GLUT-4 expression in skeletal muscle and adipose tissue. This leads to postprandial hyperglycemia and increased transfer of glucose to the fetus. Progesterone also reduces hepatic insulin sensitivity and induces hepatic triglyceride lipase activity, augmenting gluconeogenesis and hyperlipidemia, thereby further adding to hyperglycemia [26].

The present study revealed that serum levels of estradiol and progesterone were progressively increased with advancing gestational age when compared with non-pregnant group reaching a high level in late pregnancy. On the other hand, we found that their serum levels dropped significantly in 1st day post-partum. These results are in accordance with those of many investigators [32].

These hormonal changes during pregnancy may contribute to the development of insulin resistance as we found a significant positive

correlation between estradiol, progesterone and insulin resistance.

The 3rd possible explanation for the changes in plasma apelin levels during pregnancy is the changes in tumor necrosis factor α (TNF α) level during pregnancy.

During pregnancy, TNF-α was found in placental syncytiotrophoblast, decidua, and amniotic fluid .TNF-α production is greater in omental than subcutaneous adipose tissue in non-pregnant individuals, , while in pregnancy placental TNF-α production exceeds that of omental and subcutaneous adipose tissue .Thus, the placenta is most likely responsible for the increased TNF-α concentrations that can be observed during normal human pregnancy [33].

There are two types of receptors for TNF-α, named TNFR1 and TNFR2 TNFR1 is constitutively expressed throughout many tissues, including adipocytes, liver, endothelial cells, granulocytes, and the placenta, while TNFR2 is localized to immune cells. There is also a soluble form of the TNF-α receptor (s TNFR). TNF-α does not cross the placenta [34].

TNF-α induces the expression of apelin leading to an increase its circulating level via phosphatidylinositol 3-kinase (PI3K), c-Jun N-terminal kinase (JNK) and ERK1/2 signaling pathways in adipocytes [35] till mid pregnancy but late in pregnancy this effect is accompanied by increased apelin clearance through ACE2 and opposed by insulin resistance mediated by TNF-α and increased soluble TNF receptors.

Minuz et al. [36] reported that the plasma and urinary levels of s TNFR were significantly elevated in late pregnant when compared with both non-pregnant and early pregnant groups. s TNFR acts by binding or (sequestering) and neutralizing free TNF-α, consequently TNF-α becomes no longer available to interact with innate receptors thereby its signaling is disrupted in apelin -secreting adipocytes preventing apelin secretion. thus, the s TNFR functions as a physiological attenuator of TNF-α activity by competing for ligand with cell surface receptors and facilitating clearance of TNF-α from the circulation.

The 4th possible explanation of increased serum apelin levels in early pregnancy its decrease in late pregnancy is the changes in hypoxia inducible factor -1α (HIF-1α) which is a transcription factor.

HIF-1α is a key regulator of the response to low oxygen levels, initiating transcription of numerous genes during hypoxia. It is a heterodimeric transcription factor consisting of subunit α, which is oxygen-sensitive and rapidly degraded and inactivated during normoxia, and subunit β, which is constitutively active. HIF-1 α is highly expressed in the low oxygen environment of the placenta in early gestation, playing an important role in placental development and function [37].

Many studies showed that some transcription factors such as SP1 transcription factor (SP1), HIF-1α can induce expression of both apelin and APJ mRNAs [38], other studies demonstrated that other transcriptional factors such as apelin , glucocorticoid and estrogen can affect transcription of APJ mRNA [39]. In addition, insulin is also involved in the regulation of APLNR expression [40].

5. CONCLUSION

In conclusion, the present study revealed that the serum levels of apelin were progressively increased from early to mid-pregnancy then showed a marked decrease near term. The causes of these fluctuations are multiple, complex, interrelated, still disputed and in need of further investigations.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The experimental protocol was approved by physiology department and by local medical ethics committee in faculty of medicine of Zagazig University (Institutional Review Board, IRB , ZU-IRB 1757-21-12-2014).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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