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Review Article

Vitamin D deficiency and Anaemia – A Review

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Abstract

Vitamin D deficiency has turned out to be an epidemic worldwide including India with long lasting implications. Vitamin D is found to be directly related with erythropoiesis. Association of vitamin D deficiency with different types of anaemia namely - Iron deficiency Anaemia, Sickle cell Anaemia, Haemolytic Anaemia and Anaemia of Inflamation has been reported in recent studies, though the question still remains which one predisposes the other. The role of vitamin D has been illustrated in the regulation of Hepcidin-ferroportein axis. Anaemia on the other hand is very prevalent in rural and urban Indian population where adolescent girls and women of child bearing age are mostly affected. Regular screening of vitamin D deficiency and supplementation might help to eradicate its effect of causation of anaemia. The dearth of work relating Vitamin D deficiency and anaemia is the purpose of the review.

Keywords: Vitamin D deficiency, Anaemia, Hepcidin, HbA1c, Haemoglobin.

1.Background

A significant association between vitamin D deficiency and anaemia (Sim JJ et al, 2010) have been reported throughout the world. Worldwide at any given moment, iron deficiency anaemia is prevalent than any other health problem (WHO, 2008). Vitamin D deficiency is considered to be the most common nutritional disorder in Fe deficiency anaemia throughout the world. Over 30% of world population are suffering from anaemia mainly due to iron deficiency and this figure is frequently exacerbated by other secondary infections like malaria and worm infections (Slotzfus RJ et al, 1998). Anaemia resulting from Fe-deficiency is a major problem affecting 3.5 billion people in developing countries impairing cognitive development in children.

Vitamin D deficiency prevails in epidemic proportions all over the world including Indian subcontinent, where 80% of the general population is vitamin D deficient. Routine exposure to sunlight in peak hours is not feasible for general mass mainly due to indoor activities. Subclinical vitamin D deficiency is prevalent in urban and rural areas across all socio-economic and geographic strata. Long term vitamin D deficiency increases the risk of various diseases like cancer, HTN, heart diseases, osteoporosis, ricket and tuberculosis in India (Schoor V et al, 2011). Anaemia with vitamin D deficiency is most often a hidden deficiency, with a few overt symptoms (IDPAS, 2001).

Vitamin D receptor gene is considered as one of the candidate genes for anaemia (Marwah S et al, 2012). Vitamin D appears to be associated with anaemia, one possibility is that vitamin D modulates the level of systemic cytokine production thus reducing the inflammatory milieu that leads to anaemia of chronic disorder. It has been documented both in vitro and in vivo studies that the active form of vitamin D, calcitriol is involved in haematopoiesis (Bunce CM et al, 1997) and reduction of cytokine production. Vitamin D molecule exerts its action through vitamin D receptors. Reports suggest that Vitamin D receptor polymorphism leads to vitamin D deficiency (Bhanusali AA et al, 2009).

The role of vitamin D endocrine system has been involved in a broad array of physiological system including bone mineral metabolism, modulation of immune response, erythropoiesis, cellular proliferation and differentiation. The role of vitamin D in erythropoiesis has been suggested by several clinical observations. Vitamin D receptors have been observed in bone marrow and affect bone marrow function. But there is a dearth of work contributing towards the establishment of relationship between Vitamin D deficiency and anaemia. The aim of this review is to elucidate an association of vitamin D deficiency with greater risk of anaemia.

2. Worldwide prevalence of vitamin D deficiency and anaemia

The association between anaemia and vitamin D deficiency has been confirmed from the results of National Health and Nutritional Examination Survey (NHANES) 2001 – 2006 survey. The prevalence of anaemia is being observed 11.6% in persons with deficient Vitamin D levels (Kenderick J ET AL, 2009) whereas 7.2% in subject with normal vitamin D level, thus confirming the association of anaemia and vitamin D – highlighting a correlation between vitamin D deficiency and anaemia .

The prevalence of anaemia in vitamin D deficient people has been documented worldwide. Vitamin D deficiency in anaemic people including children and adults has been reported in South East Asia (Awumey EM et al, 1998).

Low serum Vitamin D level is an important international public health problem (Palacios C and Gonzalez L, 2014; Vierucci F et al, 2013; Balasubramanian S et al, 2013). Studies show a high percentage of vitamin D deficiency in Kuwait (Alyahya K et al, 2014), Italy (vierucci F et al, 2014), Norway (Oberg J et al, 2014), India (Balasubramanian S et al, 2013) to name a few. Factors like seasonal change, latitude, fitness, adiposity; sleep time and vitamin D supplement intake (Valtuena J et al, 2013) also contribute to Vitamin D deficiency.

According to a recent study 59% of Indian women are anaemic where 7 out of 10 women had vitamin D deficiency, with the eastern region having a significantly higher prevalence at 72.12% than the rest of the country whereas 45% of women are reported to be anaemic in western India. Prevalence of anaemia was higher in northern and southern India and vitamin D deficiency was found to be the highest among the women in southern and eastern part of the country. Medical screening should be emphasized in order to early detection of these conditions (Hindustan Times, Mumbai, 17th March 2015)

Though work relating Anaemia and Vitamin D deficiency started in the year 1992 , there was not much data to substantiate their correlation until 2010. Since then there has been a positive upsurge of research work on this field around the world focusing on a very prime root cause of the two diseases. Most of the work is still concentrated in European countries.

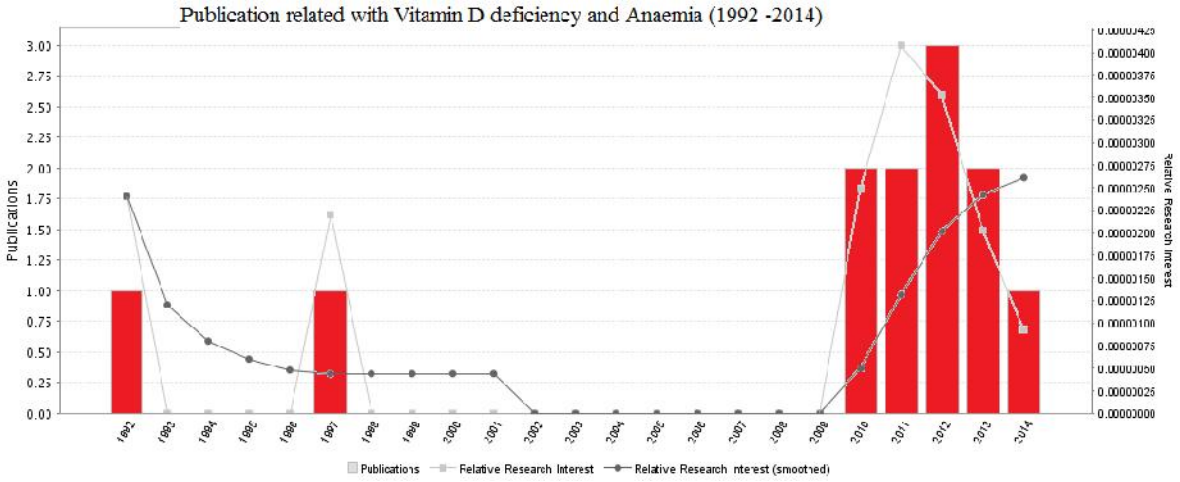
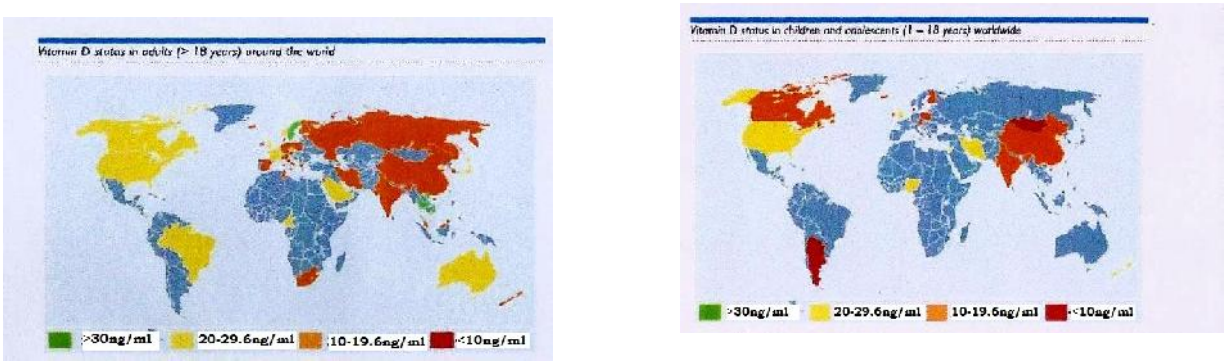


Fig 1: Graph showing the work done so far correlating Vitamin D deficiency and Anaemia (www.gopubmed.org**)**



(a) **(b)**

Fig 2: World map showing vitamin D status in the world in (a) adult population (b) in children(Interactive Maps on Vitamin D level worldwide**)**

3.Role of Vitamin D deficiency in different types of Anaemia:

3.1 Iron Deficiency Anaemia:

Iron deficiency makes a large contribution to anaemia. Iron and Vitamin D are two of the most important micronutrients for growth and development of infants specially (Suskind DL, 2009) but they are ignored frequently. Deficiency of Iron causes growth and developmental delay, cognition and memory problems, impaired immune function, frequent infections and iron deficiency anaemia (Hyun JJ et al, 2013). Iron is absorbed in small intestine and it is controlled by and dependent on body's need for iron (Munoz P and Humeres A, 2012). On the other hand body gets the required amount of vitamin D by ingestion of food or by skin exposure to ultraviolet B light for a sufficient period of time. Infants aged ≤ 24 months have been reported to have numerous adverse effects due to iron and vitamin D deficiencies (Hyun JJ et al, 2013).

Several studies in various populations all over the world suggest a high degree of association between Iron deficiency anaemia and VDD. Vitamin D receptors has already been reported in bone marrow (Kiss Z et al, 2011) and Levels of 1,25 (OH) vitamin D (active form of vitamin D) are several hundred folds higher in bone marrow compared to plasma. It imparts an important role in erythropoiesis the mechanism of RBC formation. Several mechanisms have been proposed to explain the association of vitamin D deficiency and anaemia. Vitamin D influences

Haemoglobin levels through a direct effect on erythropoiesis. Erythroid precursors are directly stimulated by vitamin D suggesting the latter's immense role in erythropoiesis. The storage and retention of Iron and reduction of pro-inflamatory cytokines is also aided by vitamin D (Bacchetta et al, 2013). Thus vitamin D deficiency reduces the ability of RBCs to become active. Vitamin D possibly modulates the level of systemic cytokine production, thus reducing the inflammatory milieu leading to anaemia of chronic diseases (Reichel H et al, 1989). Absorption of vitamin D may be impaired due to Iron deficiency in the same way it impairs fat and vitamin A intestinal absorption (Norman AW, 2006). It is still controversial which deficiency causes the other but this association should be addressed in view of better treatment proposal.

Involvement of vitamin D deficiency into the causation of Iron deficiency anaemia has been documented in recent years (Ministry of Health, WHO et al, 2002). A study suggests that infants who are exclusively breast fed have higher risk of vitamin D deficiency and insufficiency than those who are bottle fed (Abdul Razzak KK et al, 2011). In Jordanian population, Vitamin D deficiency and Iron deficiency anaemia are considered a major public health problem (Faqih AM et al, 2006). WHO estimates 52.7% of Jordanian infants and 40.76 % of the toddler are anaemic (Lawson M and Thomas M 1999). Yoon and Grindulis et. al (Grindulus H el al,1986) found a significant association of Iron deficiency anaemia and low vitamin D concentration among children <2 years of age, but no mechanism was proposed for the same.

Heldenberg et al.,(1992) reported that 1-12 months aged infants showed lower serum vitamin D due to its reduced intestinal absorption caused by Iron deficiency (Heldenberg et al, 1992). Mouse model experiments done by Katsuma et al., proved that severe IDA affects the synthesis and metabolism of iron dependent enzymes prolyl and lysyl hydroxylases and renal 25-hydroxy vitamin D 1-hydroxylase resulting in abnormal collagen synthesis and reduction in concentration of plasma 1,25dihydroxy cholecalciferol, ultimately reducing bone mineral density, thus affecting bone formation and bone reabsorption (Katsumata et al, 2009). A pilot study of Iron deficiency anaemia and vitamin D status conducted on the Tamil Nadu children in the year (2014-2015) reported that 86% of the children had inadequate sunlight exposure and 1/3 of the rural children are anaemic on WHO definition (32.3%). Exposure to sunlight is insufficient in majority of the rural children in India although overt Vitamin D deficiency is not seen here. Vitamin D deficiency awareness and the need for sunlight exposure need to be taken to general public through mass media. Consideration for more vigorous iron supplementation program particularly in women and toddler should be made mandatory by government and non government agenesis. Despite their intriguing observations there is overall paucity of clinical studies investigating whether inadequacy of vitamin D affects blood Haemoglobin level.

3.2 Sickle cell anaemia :

Correlation between vitamin D deficiency and sickle cell anaemia has been documented in various studies (Jackson TC et al 2012; Saintonge et al, 2009). Jackson TS et. al (2012) reported that children with sickle cell anaemia (SCA) are 5.3 times more likely to develop vitamin D deficiency than African –American controls. It was also estimated that 65% of the children with SCA had severe vitamin D deficiency (≤ 10ng/ml). Vitamin D supplementation for over a year in young adults with SCA and osteomalacia improved their total vitamin D level and lumbosacral and femoral bone mineral density suggesting a role of vitamin D deficiency into the pathogenesis of sickle cell disease and in India vitamin D deficiency was observed in some SCA patients (Pandey S et al., 2012). Inspite of these results it is not common practice to screen vitamin D deficiency in SCA patients. Early screening will be beneficial to prevent bone mineral complication in SCA patients.

3.3 Haemolytic anaemia:

Haemolysis leads to haemolytic anaemia when bone marrow activity cannot compensate for the increased loss of red blood cells. This can be genetic, drug induced or autoimmune. The expression of vitamin D receptors on hematon,

the buffy coating of bone marrow and the involvement of vitamin D in erythropoiesis directly relates vitamin D deficiency with haemolytic anaemia. Even patients undergoing haemodialysis have high risk of chronic haemolytic anaemia. A study conducted by Wolf M. et al,.(2007) showed that 75% of patients undergoing haemodialysis had vitamin D deficiency ranging from moderate to severe deficiency (Jackson TC et al 2012). Also children with chronic haemolytic anaemia have impaired bone health. Mouse model study by Moreau R. et al., (2012) demonstrated that anaemia is detrimental for bone health (Wolf M et al, 2007) indicating the deficiency of 25(OH)vitamin D level, as its main role is attributed to bone mineral homeostasis. But it becomes really difficult to unmask which one predisposes the other.

3.4 Anaemia of Inflamation:

Anaemia of Inflammation more specifically termed as “Anaemia of Chronic Disease” – low serum iron and low iron binding capacity in a setting of an elevated serum ferritin are the biochemical indicators of AI (Anaemia of Inflammation) (Moreau R et al, 2012). Chronic renal disease patients not requiring haemodialysis, having lower haemoglobin concentration have been associated with lower 25Hydroxy Vitamin D and higher C- reactive protein levels (Perlstein TS et al, 2014). The potential effect of vitamin D deficiency on subclinical renal diseases, remain very poorly studied and thus unexplained. The results of the study conducted by Perlstein T.S. et al., authenticate the association of vitamin D deficiency with anaemia in a cohort of older person, where vitamin D deficiency is particularly associated with classical AI (Kenderick J et al, 2009).

4. Suppression of Iron regulatory Hepcidin by Vitamin D:

Hepcidin, a peptide hormone have been recently discovered which acts as the “ master regulator” of iron homeostasis (Nemere I and Hintze K, 2008). Macrophages play a central role in iron recycling by engulfing senescent RBC (Susu M et al, 2014). Iron receptor ferroportin binds iron and retains it in macrophages with the help of hepcidin. Ferroportin is the only exporter, thus iron is internalized, degraded and iron egress from macrophages to circulation is prevented (Ganz T, 2012).

Normal recycling of iron needed for erythropoiesis is prevented as hepcidin inhibits iron egress from macrophages (Pigeon C et al, 2001; Park CH et al, 2001; Krause A et al, 2000). Hepcidin clearance from plasma is also prevented due to reduced kidney function (Caravalho C et al, 2011; Zaritsky J et al, 2009).

Recent studies suggest that vitamin D concentration are inversely proportional with hepcidin concentration and positively with haemoglobin and iron concentration (Caravalho C et al, 2011; Zaritsky J et al, 2009; Perlstein TS et al ,2011; Icardi A et al, 2013). Bacchetta and co-workers showed that vitamin D suppresses hepcidin expression in monocytes by 0.5 fold and thus proves that vitamin D deficiency directly down regulates hepcidin expression (Bacchetta J et al, 2014). In human cells, VDR (Vitamin D receptor) mediates transcription repression of HAMP (Hepcidin antibacterial protein) by suppressing its expression i.e., vitamin D directly inhibits HAMP gene for hepcidin antibacterial protein (Hewison M, 2011) transcription (Bacchetta J et al, 2014).

Elevated hepcidin and VDD are associated with anaemia in most cases of CKD, contributing to renal anaemia and pointing towards a possible role of vitamin D in iron homeostasis. Hepcidin remains elevated in CKD (Caravalho C et al, 2011; Babit JL and Lin HY, 2010)along with IL-1β and IL-6 cytokines which stimulate hepcidin production from liver and macrophages (Ganz T et al, 2008; Nemeth E et al, 2004; Lee P et al 2005; Wrighting DM and Andrews NC 2006). CKD patients require iron supplements and erythropoiesis stimulating agents (ESA) to correct disease associated anaemia (Bacchetta J et al, 2014) i.e., renal anaemia. High levels of plasma Hepcidin is common in patients with inflammation, causing intracellular sequestration of iron and thus increasing the risk of anaemia. Studies of CKD patients suggest that vitamin D status correlates directly with blood haemoglobin levels (Kalantar-Zadeh K et al, 2009).

4.1Proposed Hypothesis of vitamin D and Hepcidin – Ferroportin Iron regulatory axis :

In case of VDD , there is an elevation in the synthesis of hepcidin by hepatocytes or monocytes , increasing the systemic concentration of Hepcidin and decreasing membrane expression of Ferroportin in these cells. This results in suppression of Iron export , leading to intracellular accumulation , increased cellular ferritin, decreases systemic levels of Iron (Ganz T et al, 2008).

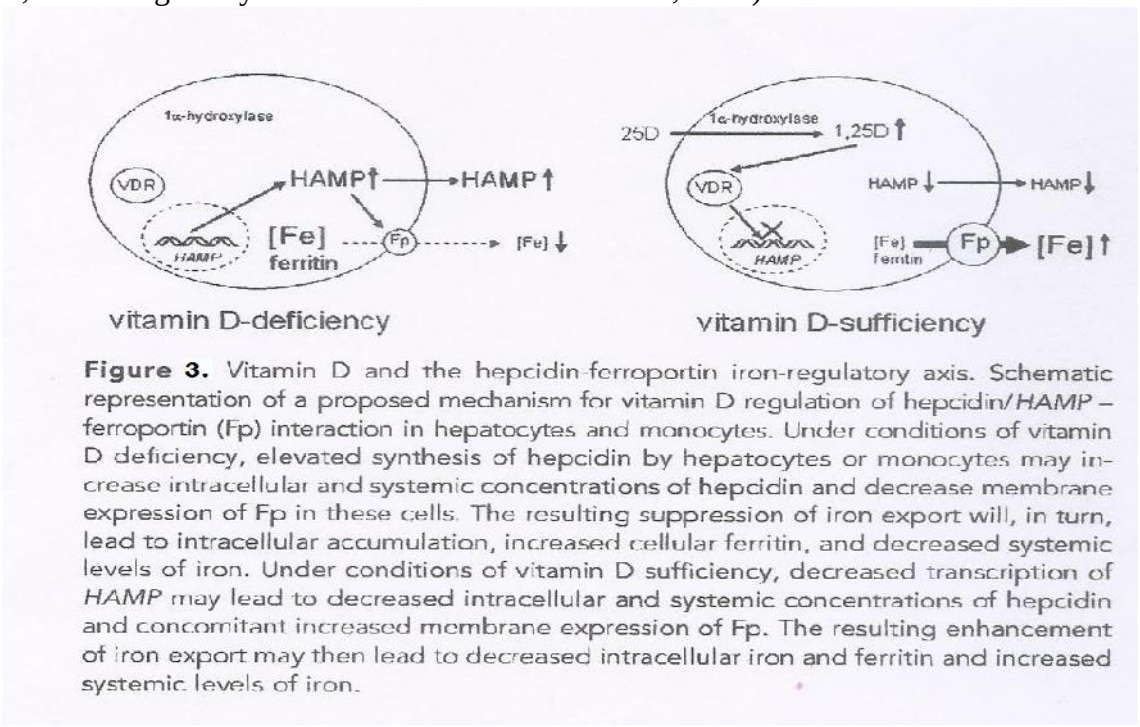


Figure 3. Vitamin D and the hepcidin-ferroportin iron-regulatory axis. Schematic representation of a proposed mechanism for vitamin D regulation of hepcidin/*HAMP* – ferroportin (Fp) interaction in hepatocytes and monocytes. Under conditions of vitamin D deficiency, elevated synthesis of hepcidin by hepatocytes or monocytes may increase intracellular and systemic concentrations of hepcidin and decrease membrane expression of Fp in these cells. The resulting suppression of iron export will, in turn, lead to intracellular accumulation, increased cellular ferritin, and decreased systemic levels of iron. Under conditions of vitamin D sufficiency, decreased transcription of *HAMP* may lead to decreased intracellular and systemic concentrations of hepcidin and concomitant increased membrane expression of Fp. The resulting enhancement of iron export may then lead to decreased intracellular iron and ferritin and increased systemic levels of iron.

Fig 3:Vitamin D and the hepcidin-ferroportin iron-regulatory axis. Schematic representation of a proposed mechanism for vitamin D regulation of hepcidin/HAMP – ferroportin (Fp) interaction in hepatocytes and monocytes (Bacchetta J et al, 2014**)**

5. Effect of Vitamin D deficiency, HbA1c and anaemia :

HbA1c is the major form of glycosylated haemoglobin. It is produced when glucose and the N terminal valine of both β chains of haemoglobin molecule react non-enzymatically (Zitterman A, 2006). The American Diabetes Association (ADA) guidelines suggests that the value of HbA1c should be kept below 7% in all diabetics (Chiu KC et al, 2004) which when greater than 7% increases the chance of progression of diabetic complications, especially micro vascular ones (Datta P et al, 2011).

According to National Health and Nutrition examination report- children and adolescents in USA who had vitamin D levels <30ng/ml were nearly twice as likely to have anaemia as those with normal vitamin D levels (Sluiter WJ et al, 1980). A relationship between Iron deficiency anaemia and HbA1c was revealed from the studies of Shuter and Mitchell et.al (1980). They attempted to explain the alteration in HbA1c levels in iron deficiency anaemia on the basis of modification of the structure of haemoglobin and levels of HbA1c in old and new red blood cells. This observation was further substantiated by Dutta P. et al (Mitchell TR et al, 1980) in Indian scenario where he clearly established a correlation between vitamin D deficiency and HbA1c. From their study a positive correlation between HbA1c and anaemia was observed. Thus anaemia is associated with high proportion of HbA1c might cause problem in the diagnosis of uncontrolled diabetes in anaemic patients. So status of vitamin D should be taken in consideration while interpreting HbA1c concentration in diabetic patients.

6. Conclusion

Thus from the studies around the world that Anaemia and Vitamin D Deficiency are positively correlated but it is still unknown if Vitamin D deficiency is the precursor to Anaemia or vice versa. Keeping the research aspect aside, it has now become very important to monitor the serum vitamin D level as well as Hb concentration of blood at regular intervals in all age groups of population. This is the only way this epidemic can be restricted. The daily requirements of vitamins and minerals should be fulfilled in order to put a check on thesediseases.Vitamin D Deficiency and its consequences are considered to be important health related problems and due to this vitamin D supplementation has also become necessary. Assessment of vitamin D related parameters such as parathyroid hormone, exposure to sunlight and dietary intake of vitamin D should be done to add more clinical information and understand the long term consequences of Vitamin D Deficiency. Continuous research should be encouraged to reveal more explanations regarding concurrent Iron deficiency and Vitamin D Deficiency. If the association could be rightly established correction of Vitamin D Deficiency levels can lead to another window for the treatment of chronic anaemia related to CKD and CLD. Lastly educational efforts are needed to increase compliance with iron and vitamin D supplementation guidelines.

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