

Does Iron Chelation by Melanin Explain the Ethnic Link with Covid-19 Fatality?

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ABSTRACT

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Introduction

There has been a great deal of comment concerning the apparent ethnic differences in the clinical outcome of Covid-19 infection and many possible factors including socio-economic influences and vitamin D levels have been discussed. However, a clear association has been observed between the death rate from Covid-19 infection and skin types IV to VI (brown to black) [1,2]. This correlation with the degree of epidermal pigmentation suggests that melanin is in some way implicated.

Epidermal Melanin

Melanin is a polymeric pigment derived from the oxidation of tyrosine, a process that takes place in specialised pigment-generating cells (melanocytes) where it is deposited in pigment granules (melanosomes) and transferred to surrounding cells. In the case of skin pigmentation, the melanin granules are continuously synthesised by epidermal melanocytes and transferred to the adjacent epidermal cells. The degree of skin pigmentation is a function of several genetically determined factors including the rate of melanin synthesis, the size of the melanin granules and the number of melanin granules transferred to epidermal cells [3].

Properties of Melanin

An important property of melanin is its strong light absorbance, and epidermal pigment takes part in several significant photoprotective processes such as scavenging of both oxidising and reducing free radicals [4].

Another notable property of melanin is its powerful metal-chelating characteristic [5-9]. As the epidermal cell population is

constantly turning over, being lost by surface desquamation [10], there is continuous replacement of epidermal pigment. Thus, the turnover of epidermal melanin provides an excretory pathway for metals, and it has been suggested that the ability of melanin to bind heavy metals and sequester them within a segregated compartment that is ultimately shed from the skin surface may act as a detoxification mechanism with significance to hominid evolution [11,12]. Many metals have been shown to be bound to melanin, including zinc and copper [13,14], and their trans-epidermal loss may be relevant, since zinc is known to have a role in anti-viral action [15] so that its melanin-linked elimination may be significant.

Iron Chelation by Melanin

However, we propose that a more important candidate in relation to the vulnerability to Covid-19 infection is iron because of the marked affinity of eumelanin for iron. For example, Liu, et al. [16] recorded a 400-fold increase in iron uptake by Sepia melanin granules exposed to a solution of ferric chloride and Fe⁺⁺ is known to be even more strongly bound to melanin. Also, as anticipated, it has been shown that the amount of iron in the epidermis is influenced by the degree of melanisation. For example, it has been shown that three times as much iron was present in sun-exposed compared to sun-shielded skin [17].

Melanin-Bound Iron Excretion and Iron Homeostasis

An investigation of iron metabolism has demonstrated that trans-epidermal iron elimination accounts for 20–25% of the daily iron loss [18]. Therefore, the degree of epidermal pigmentation

constitutes a fundamental regulatory factor in iron homeostasis by influencing the extent of trans-epidermal iron loss.

Susceptibility to Hypoxia

Thus, our proposal is that due to melanin-bound iron loss, raised levels of epidermal pigmentation increase the susceptibility to lower homeostatic iron levels. As a result of this, depending on other relevant factors such as dietary iron intake, skin type IV-VI individuals incur an increased risk of iron-deficiency anaemia and this renders them more vulnerable to the hypoxic conditions caused by the respiratory effects of Covid-19 infection [19,20].

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