HIV/AIDS-associated tryptophan depletion as part of the influence of inflammatory mediators on general nutritional status

The essential amino acid tryptophan cannot be synthesised in the body and must be acquired through dietary intake. Tryptophan is an important substrate for protein synthesis and for synthesis of the neuroactive substances serotonin, melatonin and tryptamine. Excess tryptophan, i.e., levels above the requirement for protein and serotonin synthesis, is metabolized in the kynurenine pathway under influence of the liver-specific enzyme L-tryptophan 2,3-dioxygenase. Tryptophan metabolism in the kynurenine pathway can, however, also be accelerated by the enzyme indoleamine 2,3-dioxygenase (IDO). IDO is stimulated by pro-inflammatory mediators and is independent of tryptophan levels. In other words, tryptophan metabolism can continue even during tryptophan deficiency. Studies in developed countries showed tryptophan metabolism under influence of IDO to be the main cause of tryptophan depletion in HIV/AIDS populations. Far less is known about it in developing countries. The present study investigated tryptophan depletion in context of the inflammatory and general nutritional status in a low-income South African HIV/AIDS population.

In line with studies on HIV/AIDS populations from developed countries, the present study showed a decline in the levels of tryptophan. Tryptophan levels decreased as immunodeficiency worsened (decline in CD4 counts). The decline in tryptophan levels further correlated with increases in the levels of pro-inflammatory mediators. This is in agreement with the concept of increased inflammation-driven tryptophan oxidation as the major cause of tryptophan depletion in HIV/AIDS. However, tryptophan levels in our low-income sub-Saharan HIV/AIDS population were markedly lower. In fact, patient tryptophan levels were almost half that of their healthy control counterparts and on average more than 25 percent lower than that reported for developed countries. It is feasible to assume that malnutrition may have contributed, but unlikely that it could have been the sole explanation for the difference. Pro-inflammatory activity, i.e., the main driver behind tryptophan breakdown in the kynurenine pathway, was subsequently compared to that reported for HIV/AIDS populations from the developed world. At comparable levels of immune deficiency, inflammatory activity was indeed much higher in the low income sub-Saharan population of the present study. At least two explanations for the higher pro-inflammatory activity in our population are feasible. The first is a higher prevalence of clinical and subclinical co-infections in developing countries, and the second the fact that malnutrition in itself can cause an increase in the levels of inflammatory mediators.

In the second part of the study tryptophan depletion was examined in context of the nutritional status. The effect of inflammation on nutritional status, i.e., disease-related malnutrition, is well-described in recent literature. Several studies have been performed on the nutritional status of patients with HIV/AIDS. Unfortunately, most studies ignored the effects of inflammatory mediators on the nutritional profile. The decline in nutritional status is thus generally ascribed to dietary

insufficiencies and AIDS-related gastrointestinal absorption problems. In the present study the effects of the HIV-induced inflammation on indicators of the nutritional profile, such as albumin, the albumin/globulin ratio, haemoglobin, red cell distribution width and body-mass-index, were confirmed by correlations with levels of pro-inflammatory markers. Significant correlations were also found between tryptophan levels and the levels of these nutritional markers. It is clear that tryptophan depletion as a result of increased oxidation in the kynurenine pathway forms part of the general immune-induced alterations in the nutritional profile.

Tryptophan levels in this low-income sub-Saharan HIV/AIDS population are markedly lower than that of populations from developed countries. The main cause is the higher levels of pro-inflammatory activity at comparable levels of immune deficiency. Tryptophan depletion, due to pro-inflammatory activity, forms part of the much wider effect of pro-inflammatory activity on the nutritional profile of HIV/AIDS patients.

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