



## Are we Missing Hypothyroidism in Sickle Cell Disease?

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### Clinical Image

Sickle Cell Disease (SCD) is a group of inherited hemoglobin disorders caused by a structurally abnormal variant of hemoglobin that is related to abnormal  $\beta$ -globulin genes [1,2]. This disorder affects about 1 out of every 600 African Americans and up to 3% of births in sub-Saharan Africa. Phillips et al. [1] described three cases of hypothyroidism in patients with SCD. The etiology of hypothyroidism in SCD is not clear but may be related to iron overload from multiple blood transfusions.

The prevalence of hypothyroidism in SCD is also unknown. The aim of our study was to evaluate the prevalence of hypothyroidism in SCD and determine how its diagnosis may be missed due to unreliable immunoassay (IA) methods for the measurement for thyroid hormones.

Van Deventer et al. [3] and Jonklaas et al. [4] have demonstrated how poorly IA methods for thyroid hormone measurement correlate with TSH. Moreover, Masika et al. [5] have shown that the measurement of total T3 (TT3) by IA at low concentrations is unreliable and may miss about 50% of patients with elevated TSH's and low TT3's.

We assessed 73 randomly selected patients with SCD, 17 of them (prevalence of 23.3%) having elevated TSH's ( $>4.20$  uIU/mL with a mean and median of 8.88 uIU/mL and 5.25 uIU/mL respectively. Our reference interval for TSH is 0.27 – 4.20 uIU/mL). Previously the prevalence of hypothyroidism in SCD was never documented.

Reliable laboratory evaluation of thyroid in SCD becomes even more important as in these patients the symptoms of hypothyroidism may not be obvious. For example in the case of cold intolerance it is of interest to note that most SCD patients avoid cold temperatures because this can precipitate a crisis. With constipation, another symptom of hypothyroidism we have discovered that many SCD patients take stool softeners as they are on narcotics. Depression another symptom is again hidden as many SCD patients take anti-depressants for pain control reasons. The clinical laboratory therefore plays a central role in diagnosis by measuring thyroid hormones accurately and precisely by isotope dilution LC-MS/MS.

Our results showed that in SCD patients with significantly elevated TSH's 10% of IA vs. 70% of LC-MS/MS TT3's were below the 2.5<sup>th</sup> percentile (Figure 1A). For total T4 (TT4) measurements 14.3% of IA's and 43% of LCMSMS results were below the 2.5<sup>th</sup> percentile (Figure 1B). It is worth emphasizing that it is T3 that binds avidly to the nuclear receptor and not T4 [5]. Using TT3 and/or TT4, IA concurred with the elevated TSH's 11% of the time while MS concurred 72% of the time.

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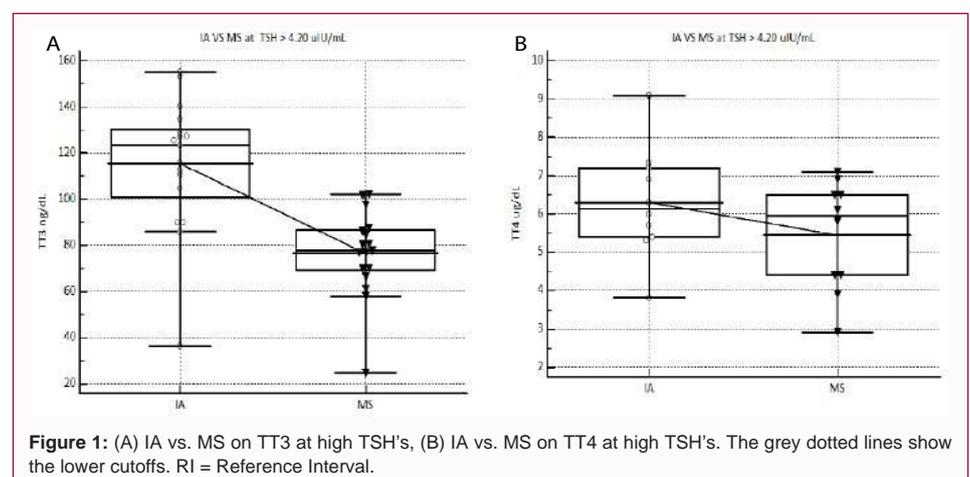


Figure 1: (A) IA vs. MS on TT3 at high TSH's, (B) IA vs. MS on TT4 at high TSH's. The grey dotted lines show the lower cutoffs. RI = Reference Interval.

This emphasizes how unreliable IA is in thyroid diagnosis in SCD and how it may cause physicians to miss patients with low thyroid hormones. The lack of correlation of the IA's for TT3 and TT4 with TSH may explain why historically very few cases of hypothyroidism have been recognized in patients with SCD.

This is a preliminary study and needs to be confirmed in a larger cohort of patients. Furthermore there is a future need to study the pathogenesis of hypothyroidism in SCD. Clearly LC-MS/MS will play an important role in highlighting the true prevalence and pathogenesis of hypothyroidism in the SCD population.

In conclusion we recommend that SCD patients with elevated TSH's have their thyroid hormone measurements performed with reliable methods such as LC-MS/MS, thereby allowing physicians to evaluate whether thyroid hormone replacement therapy needs to be implemented.

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