SQU Med J, April 2009, Vol. 9, Iss. 1, pp. 37-41, Epub 16th mar 2009
Submitted - 21st May 08
Revision Req. 4th Aug 08, Revision Recd. 4th Nov 08,
Accepted - 23rd Dec 08

Serum Myoglobin in Patients with Thyroid Dysfunction

*Waad-Allah S Mula-Abed, Sawsan S Al-Sinani, Huda S Al-Hashmi

مايوغلوبين مصل الدم لدى المرضى المصابين باضطراب وظيفة الغدة الدرقية

وعد الله شريف ملا عبد، سوسن سالم السناني، هدى سعيد الهاشمي

الملخص: الهدف: تقييم نمط التغير في مستوى مايوغلوبين مصل الدم لدى المرضى المصابين باختلال وظيفة الغدة الدرقية . **الطريقة:** تم فحص عينات للمصل من 150 مريضا (35 ذكرا و115 أنثى) مصابا باختلال وظيفة الغدة الدرقية من المحولين إلى المستشفى السلطاني بمسقط (سلطنة عمان). كان مدى أعمارهم يتراوح بين 14 - 56 سنة (كان المعدل ± الانحراف المعياري 34.3 ± 12.7 سنة) . تم تصنيف المرضى وفق نتائج فحص الغدة الدرقية الوظيفية الهرمون المنبه للغدة الدرقية وهرمون الدرقية الحر) إلى ثلاث مجاميع (50 شخصا لكل منها): المصابون بانخفاض وظيفة الغدة الدرقية . المصابون بفرط نشاط الغدة الدرقية والأشخاص ذوي الفعالية الطبيعية للغدة الدرقية . **النتائج:** كان متوسط مستوى مايوغلوبين مصل الدم مرتفعا لدى المصابين بانخفاض وظيفة الغدة الدرقية مقارنة بالمصابين بفرط نشاط الغدة الدرقية والأشخاص الأصحاء (كان المتوسط + الانحراف المعياري للمايوغلوبين بالتعاقب +23.1 38.5 مقابل +7.0 18.1 و 5.7 + 17.4 مايكروغرام /لتر) . وكان هناك فرقا معتدا إحصائيا ((F= 36.1, p < 0.001) في متوسط المايوغلوبين بين المصابين بانخفاض وظيفة الغدة الدرقية والأصحاء . بينما لم يلاحظ أي فرق معتد إحصائيا بين المصابين بفرط نشاط الغدة الدرقية ومجموعة الأصحاء . عندما تم حساب المتوسط + انحرافين معياريين للمايوغلوبين عند الأصحاء كان المدى المرجعي 6-29 مايكرو غرام/ ليتر. أظهرت الدراسة أيضا أن 29 مريضا (58%) من المصابين بانخفاض وظيفة الغدة الدرقية كان لديهم تركيز المايوغلوبين عاليا . بينما كان تركيزه طبيعيا لدى الآخرين (21 مريضا –42%) . لم يلاحظ ارتباطا معتدا إحصائيا بين الهرمون المنبه للغدة الدرقية أو هرمون الدرقية الحر والمايوغلوبين عند كل الأشخاص تحت الدراسة . **الخلاصة:** لوحظ ارتفاع مايوكلوبين مصل الدم لدى معظم المصابين بانخفاض وظيفة الغدة الدرقية . ولهذا يجب التفكير جديا بوضع انخفاض وظيفة الغدة الدرقية ضمن التشخيص التفريقي للأشخاص الذين يكون لديهم ارتفاعا في تركيز المايوغلوبين في مصولهم .

مفتاح الكلمات: مايوغلوبين . انخفاض وظيفة الغدة الدرقية.

ABSTRACT ***Objectives:*** To assess the pattern of change in serum myoglobin concentration in subjects with thyroid dysfunction. ***Methods:*** Serum samples were selected from 150 subjects with suspected thyroid disorder who were referred to the Royal Hospital, Muscat, Oman. The subjects were 35 males and 115 females, aged 14-56 years with mean ± SD of 34.3 ± 12.7 years. They were classified on the basis of thyroid stimulating hormone (TSH) and free thyroxine (FT4) into 3 groups, each consisting of 50 subjects: hypothyroid, hyperthyroid, and euthyroid subjects. ***Results:*** The mean serum myoglobin concentration was higher in hypothyroid patients compared to hyperthyroid and euthyroid subjects (mean ± SD was 38.5 ± 23.1 µg/L in hypothyroid; 18.1 ± 7.0µg/L in hyperthyroid; 17.4 ± 5.7µg/L in euthyroid). There was a significant difference in myoglobin concentration between hypothyroid and euthyroid groups ($F = 36.1$, $p < 0.001$), however, there was no significant difference between the hyperthyroid and euthyroid groups. When the mean ± 2SD for myoglobin in euthyroid subjects was calculated, the reference range was 6-29 µg/L. Of the hypothyroid subjects, 29 (58%) had high myoglobin and 21 (42%) had normal myoglobin level. No significant correlation was noticed between TSH or FT4 and myoglobin in all studied subjects. ***Conclusion:*** Raised serum myoglobin may be observed in patients with hypothyroidism. Hence hypothyroidism should be considered in the differential diagnosis of patients with raised serum myoglobin concentration.

Key words: Myoglobin; Hypothyroidism.

Advances in Knowledge

- Elevated myoglobin values can occur following muscle involvement or damage in patients with myopathy or transiently following cardiac ischaemia.

Department of Chemical Pathology, Royal Hospital, Muscat, Sultanate of Oman

**To whom correspondence should be addressed. Email: drsharef@omantel.net.om*

- Myopathy may develop due to a variety of diseases including endocrine dysfunction such as hypothyroidism.
- Thyroid dysfunction is common and screening for it is now commonly followed in clinical practice.
- Hypothyroidism should be considered in the differential diagnosis of patients with myopathy or raised serum myoglobin concentration.

Applications to Patient Care

- Patients with hypothyroidism may rarely develop muscle damage in the form of asymptomatic elevation of muscle markers, myopathy or even rhabdomyolysis.
- This involvement may occur especially in undiagnosed cases, those with poor drug compliance, or in combination with other aggravating factors such as statin therapy.
- Such a link is of particular consideration due to the large number of patients taking statin drugs nowadays.
- Hypothyroidism should be considered in the differential diagnosis of patients with myopathy or raised serum myoglobin concentration, even if there is another disease, mechanism or therapy explaining its elevation.

Myoglobin is a cytoplasmic protein in striated cardiac and skeletal musculature that is involved in oxygen transport and storage within the myocytes. Besides troponin, myoglobin determination in serum may play a contributing step in the diagnosis of myocardial ischaemia particularly acute myocardial infarction.[1, 2] Elevated myoglobin values can also occur after skeletal muscle damage in patients with myopathy and in those with marked renal impairment.[3]

Disorders of thyroid function are common and are now considered in the differential diagnosis of patients with a wide variety of symptoms. The prevalence of hypothyroidism was 3.7% and that of hyperthyroidism was 0.5% in the United States general population in a 1999-2002 survey.[4] The prevalence of thyroid dysfunction is even higher in the elderly,[5] many having subclinical thyroid dysfunction with controversial recommendations for treatment thresholds balanced on the risk to target organs particularly the heart and bone.[6] Hence, screening for thyroid problems is now commonly followed in clinical practice.[7] However, although biochemical screening for thyroid disorders is usually followed, particularly in the elderly, the clinical diagnosis of hypothyroidism should also be considered in patients with unexplained persistent elevations of serum muscle enzymes. A significant increase in these enzymes may occur in basal conditions and is gradually normalised by substitution therapy.[8, 9]

The objective of this study was to assess the pattern of change in serum myoglobin concentration in patients with thyroid disorders, both hypothyroidism and hyperthyroidism, and to compare them with euthyroid subjects.

METHODS

In this study, 150 tests from routine sampling were selected on the suspicion of thyroid disorders and underwent a thyroid function test (TFT), which included measurement of free thyroxine (FT4) and thyroid stimulating hormone (TSH). The study was a naturalistic observation, an integral part of routine clinical procedure. The blood samples for these subjects were selected from those referred to the Department of Chemical Pathology, Royal Hospital, Muscat, Oman, for TFT during a period of 6 months (1 Jan to 30 June 2007). The criteria for selection included patients with no other diseases or abnormal clinical or laboratory tests other than thyroid related problems. Of these subjects, 32 were referred from the Outpatient Department at the Royal Hospital and 118 were from Primary Health Centres within the Muscat Region. The subjects were 35 males and 115 females, aged 14-56 years with mean ± SD of 34.3 ± 12.7 year. They included 50 patients with hypothyroidism (12 males, 38 females, aged 20-56 years, 38.0 ± 13.9 years), 50 patients with hyperthyroidism (15 males, 35 females, aged 14-56 years with 34.0 ± 10.6 years), and 50 subjects with euthyroid state (8 males, 42 females,

Table 1: Serum thyroid stimulating hormone (TSH), free thyroxine (FT4) and myoglobin in the studied groups.

Analyte	Euthyroid		Hypothyroid		Hyperthyroid	
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
TSH (mU/L)	1.339	0.958	71.113	32.323	0.0036	0.0023
FT4 (pmol/L)	14.00	2.26	6.52	2.149	40.57	17.04
Myoglobin (µg/L)	17.4	5.7	38.5	23.1	18.1	7.0

aged 15-54 years, 32 ± 12.4 year). Hypothyroidism was defined as raised TSH (>10.0 mU/L) with low (or low-normal) FT4, while hyperthyroidism was defined as suppressed TSH (<0.010) with raised FT4. [10]

All serum samples were assayed for FT4 and TSH, and following the definition of the subject as hypothyroid, hyperthyroid or euthyroid, serum was then assayed also for myoglobin. Serum FT4 and TSH were measured by a chemiluminescent microparticle immunoassay (CMIA) on the Architect 2000 System (Abbott, USA).[11, 12] The TSH assay is an ultrasensitive third generation assay with analytical sensitivity of 0.003 mU/L. Serum myoglobin was measured by an electrochemiluminescence immunoassay (ECLIA) on the Roche Cobas e 411 immunoassay analyser (Roche/Hitachi, Germany).[13]

The statistical methods included descriptive statistical analyses that comprise the mean, standard deviation (SD), and range (minimum-maximum). One-sample Kolmogorov-Smirnov analysis was used for identifying the pattern of distribution of myoglobin in each group while one way ANOVA (one way analysis of variance) was used to compare the differences in the means of myoglobin concentrations between the groups. A correlation study was also done to compare between myoglobin and TSH or FT4 concentrations.[14] Statistical significance was assigned for p <0.05.

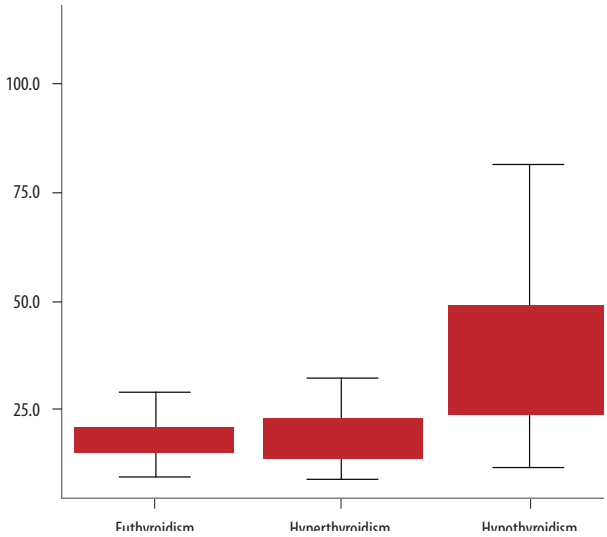

Figure 1: Distribution of myoglobin in euthyroid, hypothyroid, and hyperthyroid groups (bars represent mean ± 1SD).

RESULTS

The results of data analysed are presented according to the grouping of subjects based on TFT as in Table 1. The use of one-sample Kolmogorov-Smirnov analysis revealed a normal distribution in serum myoglobin concentration in each of the three groups. One way ANOVA revealed a significant difference (F = 36.1, p <0.001) in means of myoglobin concentrations between the hypothyroid (38.5 ± 23.1 µg/L) and euthyroid (17.4 ± 5.7 µg/L) groups. However, there was no significant difference in mean serum myoglobin concentration between the hyperthyroid and euthyroid groups.

When the mean ± 2SD for myoglobin concentration in the euthyroid subjects was calculated (Figure 1), the reference range was 6-29 µg/L. Of the hypothyroid subjects, 29 (58%) had a high myoglobin and 21 (42%) had a normal myoglobin level. No significant correlation was noticed between TSH or FT4 and myoglobin in all studied subjects (p> 0.05). The distribution of serum myoglobin in the studied subjects is shown in Figure 1.

DISCUSSION

Biochemical screening using different organ profiles, including TFT, is frequently performed for patients consulting clinics or hospitals as part of health care provision. Subclinical or overt hypothyroidism or hyperthyroidism are commonly diagnosed in clinical practice.[4, 5, 7]

In this study, hypothyroid patients showed signifi-

cantly higher mean myoglobin levels in comparison with hyperthyroid or euthyroid subjects. Serum myoglobin levels were higher than the reference range in the euthyroid group in 58% of the hypothyroid patients. This may be explained on the basis that, depending on the degree of hormone deficiency, skeletal muscle involvement may occur in hypothyroidism. Creatine kinase and myoglobin have been proved to be useful indicators of myopathy including that due to hypothyroidism.[15, 16] They are sensitive for the early detection of muscle involvement due to the metabolic disorder and are closely correlated with the metabolic states of patients.[16] Another possible mechanism for raised myoglobin in patients with hypothyroidism may be explained by an underlying autoimmune process whereby muscle protein antibodies, especially to myoglobin, myosin and troposin, are frequently present in patients with autoimmune thyroid disease leading to muscle damage.[17]

In comparison with other studies, Mortino et al.[18] observed significantly higher serum myoglobin levels in long-term and short-term hypothyroid patients (examined 20 days after withdrawal of thyroid replacement therapy) than normal controls, with a significant inverse correlation between thyroid hormones and myoglobin levels in long-term, but not short-term, hypothyroids. Normalisation of myoglobin levels following thyroxine replacement was achieved earlier than serum TSH, hence, the duration and severity of hypothyroidism are important factors in the rise of myoglobin. Roti et al.[19] also reported high and low serum concentrations of myoglobin, creatine kinase and lactate dehydrogenase in hypothyroid and hyperthyroid patients respectively. They confirmed that the muscle (not cardiac) isoenzymes are the source of increased enzyme activity, a finding that was also confirmed by Giampietro et al.[16] In our study, as in other reports,[16, 20] despite the high serum myoglobin concentrations observed in hypothyroidism, no significant correlation was noted between TSH and the muscle markers, creatine kinase or myoglobin. Also, in our study, the hyperthyroid patients clearly exhibited myoglobin levels very approximate (with no significant difference) to those of euthyroid subjects. However, this finding was not in accord with that of Wan Nazainmoon et al. [21] who found that in both overt and subclinical hyperthyroid patients, serum creatine kinase levels were significantly lower than euthyroid or hypothyroid patients.

It seems that patients with hypothyroidism may occasionally be prone to muscle damage leading to myopathy or even rhabdomyolysis which can be attributed to undiagnosed hypothyroidism. The spectrum of presentation, as a consequence of muscle involvement, may be in the form of asymptomatic elevation of muscle markers, myopathy, rhabdomyolysis or even acute renal failure. Muscle functions usually completely recover with thyroxine therapy.[22, 23, 24] Studies, such as those reported by Sekine et al. [25] suggest that rhabdomyolysis could also occur in patients with hypothyroidism, especially those with poor drug compliance, in combination with other aggravating factors such as exercise. Recently, Kursat et al.[26] and Kiernan et al.[27] reported an important link between statin induced rhabdomyolysis and hypothyroidism, both overt and occult forms. Such a link or aggravating factor is of particular concern due to the large number of patients taking statin drugs nowadays worldwide. Hence, statin, when prescribed as a hypolipidaemic drug for patients with dyslipidaemia and an associated or underlying hypothyroidism, may raise their risk for muscle involvement, which is a recognised side effect of statin,[28, 29] and also may rarely raise their requirement for thyroxine therapy.[27]

CONCLUSION

Raised serum myoglobin may be observed in patients with hypothyroidism. Hence, hypothyroidism should be considered in the differential diagnosis of patients with raised serum myoglobin concentration, even if there is another disease, mechanism or therapy explaining its elevation.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the support of the Royal Hospital, Muscat, for their research.

CONFLICT OF INTEREST: None

REFERENCES

1. Mair J, Puschendorf B. Current aspects in the laboratory diagnosis of acute myocardial infarction. Lab Med 1995; 19:304-18.

2. Bakker AJ, Koelemay MJ, Gorgels JP, van Vlies B, Smits R, Tijissen JG, et al. Troponin T and myoglobin at admission: value of early diagnosis of acute myocardial infarction. Eur Heart J 1994; 15:45-53.

3. Ohman EM, Casey C, Bengston JR, Pryor D, Tormey W, Horgan JH. Early detection of acute myocardial infarction: additional diagnostic information from serum

concentrations of myoglobin in patients without ST elevation. Br Heart J 1990; 63:335-8.

4. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffer KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999-2002). Thyroid 2007; 17:1211-23.

5. Empson M, Flood V, Ma G, Eastman CJ, Mitchell P. Prevalence of thyroid disease in an older Australian population. Intern Med J 2007; 37:448-55.

6. Biondi B, Cooper DS. The clinical significance of subclinical thyroid dysfunction. Endocr Rev 2008; 29:76-131.

7. Vanderpump MPJ, Tunbridge WMG, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community; a twenty-year follow up of the Whickham survey. Clin Endocrinol (Oxf) 1995; 43:55-68.

8. Burnett JR, Crooke MJ, Delahunt JW, Feek CK. Serum enzymes in hypothyroidism. N Z Med J 1994; 107:355-6.

9. Minutiello L. The enzymatic and electrocardiographic changes falsely indicative of an acute myocardial infarct during hypothyroidism. Minerva Cardioangiol 1993; 41:597-602.

10. Ladenson PW, Singer PA, Ain KB, Bagchi N, Bigos ST, Levy EG, et al. American Thyroid Association Guidelines for detection of thyroid dysfunction. Arch Intern Med 2000; 160:1573-5.

11. Sturgess ML, Weeks I, Evans PJ, Mpoko CN, Laing I, Woodhead JS. An Immunochemiluminometric assay for serum free thyroxine. Clin Endocrinol 1987; 27:383-93.

12. Hay ID, Klee GG. Linking medical needs and performance goals: clinical and laboratory perspectives on thyroid disease. Clin Chem 1993; 39:1519-24.

13. Lee HS, Cross SJ, Garthwaite P, Dickie A, Ross I, Walton S, et al. Comparison of the value of novel rapid measurement of myoglobin, creatine kinase, and creatine kinase MB with the electrocardiogram for the diagnosis of acute myocardial infarction. Br Heart J 1994; 71:311-5.

14. Hill AB, Hill ID. Bradford Hill's Principles of Medical Statistics. 12th Ed. London: Hodder Arnold, 1991.

15. Finsterer J, Stollberger C, Corossegger C, Kroiss A. Hypothyroid myopathy with unusually high serum creatine kinase values. Horm Res 1999; 52:205-8.

16. Giampietro O, Clerico A, Buzzigoli G, Del Chicca MG, Boni C, Carpi A. Detection of hypothyroid myopathy by measurement of various serum muscle markers-myoglobin, creatine kinase, lactate dehydrogenase and their isoenzymes. Correlations with thyroid hormone levels (free and total) and clinical usefulness. Horm Res 1984; 19:232-42.

17. Ruchala M, Kasowicz J, Baumann-Antczak A, Skiba A, Zamyslowska H, Sowinski J. The prevalence of autoantibodies to: myosin, troponin, tropomyosin and myoglobin in patients with circulating triiodothyronine and thyroxine autoantibodies. Neuro Endocrinol Lett 2007; 28:259-66.

18. Mortino E, Sardano G, Vaudagna G, Bambini G, Breccia M, Motz E, et al. Serum myoglobin in primary hypothyroidism and effect of L-thyroxine therapy. J Nucl Med 1982; 23:1088-92.

19. Roti E, Bandini P, Robuschi G, Emanuele R, Ciarlini E, Buzzonetti P, et al. Serum concentrations of myoglobin, creatine kinase, lactate dehydrogenase and cardiac isoenzymes in euthyroid, hypothyroid and hyperthyroid subjects. Ric Clin Lab 1980; 10:609-17.

20. Mula-Abed WS, Al-Naemi AH. Validity of serum creatine kinase activity in the diagnosis of thyroid disorders. J Bahrain Med Soc 2005; 17:14-17.

21. Wan Nazainmoon WN, Siaw FS, Sheriff IH, Faridah I, Khalid BAK. Serum creatine kinase: an adjunct biochemical index of subclinical thyrotoxicosis. Ann Clin Biochem 2001; 38:57-8.

22. Kisakol G, Tunc R, Kaya A. Rhabdomyolysis in a patient with hypothyroidism. Endocr J 2003; 50:221-3.

23. Kar PM, Hirani A, Allen MJ. Acute renal failure in a hypothyroid patient with rhabdomyolysis. Clin Nephrol 2003; 60:428-9.

24. Birewar S, Oppenheimer M, Zawada ET Jr. Hypothyroid acute renal failure. S D J Med 2004; 57:109-10.

25. Sekine N, Yamamoto M, Michikawa M, Enomoto T, Hayashi M, Ozawa E, et al. Rhabdomyolysis and acute renal failure in a patient with hypothyroidism. Intern Med 1993; 32:269-71.

26. Kursat S, Alici T, Colak HB. A case of rhabdomyolysis induced acute renal failure secondary to statin-fibrate-derivative combination and occult hypothyroidism. Clin Nephrol 2005; 64:391-3.

27. Kiernan TJ, Rochford M, McDermott JH. Simvastatin induced rhabdomyolysis and an important clinical link with hypothyroidism. Int J Cardiol 2007; 119:374-6.

28. Harper CR, Jacobson TA. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. Curr Opin Lipidol 2007; 18:401-8.

29. Kobayshi M, Chisaki I, Narumi K, Hidaka K, Kagawa T, Itagaki S, et al. Association between risk of myopathy and cholesterol-lowering effects: A comparison of all statins. Life Sci 2008; 82:969-75.