



# Alterations in levels of intermediate-chained acylcarnitines associate with weight-gain following reestablishment of euthyroidism in Graves' disease

Mahmoud Al Majdoub<sup>1</sup> · Mikael Lantz<sup>1,2</sup> · Peter Spégel<sup>1,3</sup>

Received: 15 May 2018 / Accepted: 23 August 2018 / Published online: 3 September 2018  
© Springer Science+Business Media, LLC, part of Springer Nature 2018

## Introduction

Graves' disease (GD) is an autoimmune disease resulting in increased production of thyroid hormones. The disease is associated with a state of relative starvation that, despite of increased hunger and food intake, result in weight loss and muscle weakness [1]. Fatty acid oxidation is increased due to a reduced sensitivity of carnitine palmitoyl transferase 1 (CPT1), a master regulator of lipid metabolism, to inhibition by malonyl-CoA [2, 3]. Moreover, increased expression and activity of this protein has been suggested in the disease [2, 3]. Hence, the disease is likely to result in exaggerated production of acylcarnitines, resulting in release of these intermediates into the circulation [4]. In line with this, two recent studies have shown a marked reduction in acylcarnitine levels, particularly of those with intermediate chain length, following reinstatement of euthyroidism in GD [5, 6].

GD is treated by anti-thyroid medication, radioiodine or surgery and depending on treatment modality may be followed by thyroid hormone replacement therapy [7]. Treatment may result in excessive weight gain, which is a major concern of the patient [8]. Hence, identification of those at

high risk for excessive weight gain could identify patients requiring supplementary life-style interventions.

Attempts have been made to predict weight regain using anthropometric and clinical features [9]. Weight changes prior to diagnosis, treatment, and length of follow up were found to be the most significant risk factors associated with weight gain [9]. Here, we examine if low baseline levels of intermediate-chained acylcarnitines is a risk factor for excessive weight gain in Swedish patients with GD. We also examine whether changes in acylcarnitine levels associate with weight gain following reinstatement of euthyroidism.

## Subjects and methods

Data on levels of nine intermediate-chained acylcarnitines, anthropometric and clinical data were collected from a previously published study [6]. Nineteen patients were initially included. One patient was excluded due to lack of BMI data. All patients were treated with methimazole 15 mg twice daily and substituted with L-thyroxine to reestablish euthyroidism (block and replace). The study was registered in the Clinical Trials.gov protocol registration system (NCT01458600).

Acylcarnitine data were log<sub>2</sub>-transformed and analyzed using linear models (R 3.5/Bioconductor and the limma package), adjusted for potential confounders. *p*-values were corrected for multiple comparisons using the FDR method. An adjusted *p*-value (*q*) < 0.05 was considered statistically significant.

## Results

Clinical data on the patients have previously been published [6], and only some key results are summarized below. A

---

**Electronic supplementary material** The online version of this article (<https://doi.org/10.1007/s12020-018-1735-9>) contains supplementary material, which is available to authorized users.

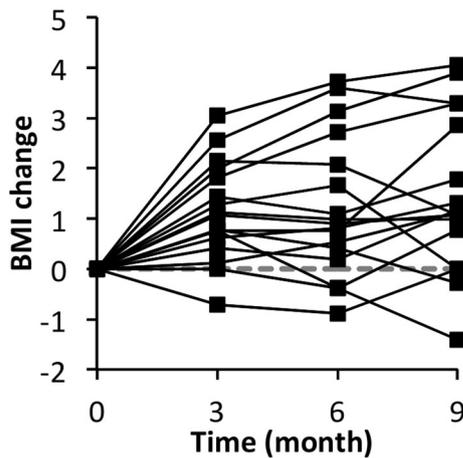
---

✉ Peter Spégel  
peter.spegel@chem.lu.se

<sup>1</sup> Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden

<sup>2</sup> Department of Endocrinology, Skåne University Hospital, Malmö, Sweden

<sup>3</sup> Department of Chemistry, Centre for Analysis and Synthesis, Lund University, Lund, Sweden



**Fig. 1** Alterations in BMI in individual patients following reestablishment of euthyroidism

transition from hyperthyroidism to near euthyroidism was achieved in all patients already at 3 months after initiation of treatment. BMI was significantly increased at 3 months and did not change at the 6 and 9 months follow up. BMI increased in 16, was unaltered in one and reduced in one of the 18 patients at the three months follow up (Fig. 1). The initial BMI gain was lost in some of the patients at the 9 months visit. Twenty-two percent of the patients were overweight at initiation of the study and by the 9 months visit this fraction had increased to 33%. Data on each individual patient is presented in Supplemental Table 1.

We could not find a significant association between baseline levels of acylcarnitines and weight changes at 3, 6, and 9 months after initiation of the treatment. However, alterations in 6 out of the 10 detected intermediate-chained acylcarnitines (8:0, 10:0, 10:1, 12:0, 12:1, and 14:2) associated with changes in BMI observed at the 3 months visit ( $q < 0.05$ ) (Table 1). Associations remained after adjustment for age, sex, baseline BMI and TSH or T4. However, associations were lost after adjustment for baseline T3, or changes in T3 between baseline and the 3 months visit. No significant association was found between alterations in acylcarnitines and BMI at the 6 and 9 months follow up.

## Discussion

Reinstatement of euthyroidism in patients with GD is associated with a highly individual weight gain, which may normalize BMI but also increase it above pre-morbid levels [9]. In our study, the prevalence of overweight was low at baseline and then approached the reported prevalence in Sweden (45% in women [10]) at the 9 months visit. We could not find an association between baseline BMI and alterations in BMI at follow ups, which is in line with a

**Table 1** Associations between alterations in acylcarnitine levels and BMI between baseline and the three months follow up

Acylcarnitine <sup>a</sup>	Unadjusted		Adjusted <sup>b</sup>		Adjusted <sup>c</sup>	
	Beta	<i>q</i>	Beta	<i>q</i>	Beta	<i>q</i>
8:0	−0.69	0.036	−0.92	0.0077	−0.91	0.0090
8:1	−0.22	NS	−0.42	NS	−0.43	NS
10:0	−0.68	0.036	−0.94	0.0077	−0.94	0.0090
10:1	−0.66	0.036	−0.85	0.0087	−0.83	0.011
10:2	−0.54	0.051	−0.67	0.029	−0.66	0.032
12:0	−0.59	0.044	−0.80	0.012	−0.79	0.014
12:1	−0.63	0.038	−0.85	0.0087	−0.83	0.011
14:0	−0.16	NS	−0.27	NS	−0.26	NS
14:1	−0.50	0.065	−0.63	0.035	−0.61	0.044
14:2	−0.57	0.045	−0.72	0.021	−0.70	0.027

NS not significant

<sup>a</sup>Acylcarnitines are named by their carbon number: number of unsaturations

<sup>b</sup>Adjusted for age, sex, and baseline BMI

<sup>c</sup>Adjusted for age, sex, baseline BMI, and baseline TSH

previous study that only showed a tendency of such an association in a much larger sample [9]. Although most international guidelines recommend titration of thyrostatics as first line treatment, the block and replace approach was used in the present study, to rapidly take control of the thyrotoxicosis.

Instead, we hypothesized that baseline levels of medium-chained acylcarnitines reflect adaptation of metabolism to the hyperthyroid state and that reinstatement of euthyroidism may overcompensate the metabolic perturbation in some individuals. To test this hypothesis, we investigated if baseline levels of intermediate-chained acylcarnitines associated with weight regain after reestablishment of euthyroidism. Whereas no such association could be proven, our data instead showed a clear negative association between alterations in levels of several acylcarnitines and changes in BMI between baseline and 3 months follow up. Our findings are supported by previous studies revealing increased plasma acylcarnitine levels after a weight loss intervention [11]. However, as obesity has been associated with increased levels of these fatty acid oxidation products [12], these results are likely to reflect an anabolic and catabolic state, respectively. Evidently, a smaller decrease in acylcarnitine levels, reflecting a maintained high rate of lipid oxidation, is expected to result in a smaller weight gain. The association was lost at the two consecutive visits, which may be explained by changes in life-style factors as a reaction to the initial weight gain. However, dose adjustment of L-thyroxin may also have an impact on the increase in weight. Limitations of the present study include lack of pre-morbid BMI data and the relatively small sample size.

Our analysis of acylcarnitines employs a relative quantification, and we do not know whether post-treatment levels reach levels observed in the healthy population.

In conclusion, alterations in acylcarnitine levels may be associated with changes in BMI in GD. In our study baseline levels of intermediate-chained acylcarnitines were not associated with treatment elicited increase in BMI. Hence, further research is required to identify markers of excessive weight gain, which would enable identification of patients at risk who would benefit from life-style interventions.

**Acknowledgements** Thanks to associate professor Bengt Hallengren for valuable discussion of the manuscript.

**Funding** This work was supported by the Royal Physiographic Society, the Novo Nordisk-, Pålsson-, the Swedish Diabetes-, Hjelt- and Crafoord Foundations, the research funds of Malmö University Hospital, the Faculty of Medicine at Lund University, the Skåne Research Foundation, the Swedish Research Council Strategic Research Area Exodiab (2009-1039) and Linnaeus grant (349-2006-237), and the Swedish Foundation for Strategic Research (IRC15-0067).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

## References

1. G. Dimitriadis, P. Mitrou, V. Lambadiari, E. Boutati, E. Maratou, E. Koukkou, D. Panagiotakos, N. Tountas, T. Economopoulos, S. A. Raptis, Insulin-stimulated rates of glucose uptake in muscle in hyperthyroidism: the importance of blood flow. *J. Clin. Endocrinol. Metab.* **93**(6), 2413–2415 (2008)
2. R.L. Mynatt, E.A. Park, F.E. Thorngate, H.K. Das, G.A. Cook, Changes in carnitine palmitoyltransferase-I mRNA abundance produced by hyperthyroidism and hypothyroidism parallel changes in activity. *Biochem. Biophys. Res. Commun.* **201**(2), 932–937 (1994)
3. M.S. Jansen, G.A. Cook, S. Song, E.A. Park, Thyroid hormone regulates carnitine palmitoyltransferase Ialpha gene expression through elements in the promoter and first intron. *J. Biol. Chem.* **275**(45), 34989–34997 (2000)
4. R.R. Ramsay, A. Arduini, The carnitine acyltransferases and their role in modulating Acyl-Coa pools. *Arch. Biochem. Biophys.* **302**(2), 307–314 (1993)
5. C.L. Chng, A.Y. Lim, H.C. Tan, J.P. Kovalik, K.W. Tham, Y.M. Bee, W. Lim, S. Acharyya, O.F. Lai, M.F. Chong, P.M. Yen, Physiological and metabolic changes during the transition from hyperthyroidism to euthyroidism in Graves' disease. *Thyroid* **26**(10), 1422–1430 (2016)
6. M. Al-Majdoub, M. Lantz, P. Spegel, Treatment of Swedish patients with Graves' hyperthyroidism is associated with changes in acylcarnitine levels. *Thyroid* **27**(9), 1109–1117 (2017)
7. C.M. Girgis, B.L. Champion, J.R. Wall, Current concepts in graves' disease. *Ther. Adv. Endocrinol. Metab.* **2**(3), 135–144 (2011)
8. S. Jansson, G. Berg, G. Lindstedt, A. Michanek, E. Nyström, Overweight - a common problem among women treated for hyperthyroidism. *Postgrad. Med. J.* **69**, 107–111 (1993)
9. J. Dale, J. Daykin, R. Holder, M.C. Sheppard, J.A. Franklyn, Weight gain following treatment of hyperthyroidism. *Clin. Endocrinol.* **55**(2), 233–239 (2001)
10. M. Ng, T. Fleming, M. Robinson, B. Thomson, N. Graetz, C. Margono, E.C. Mullany, S. Biryukov, C. Abbafati, S.F. Abera, J. P. Abraham, N.M. Abu-Rmeileh, T. Achoki, F.S. AlBuhairan, Z. A. Alemu, R. Alfonso, M.K. Ali, R. Ali, N.A. Guzman, W. Ammar, P. Anwari, A. Banerjee, S. Barquera, S. Basu, D.A. Bennett, Z. Bhutta, J. Blore, N. Cabral, I.C. Nonato, J.C. Chang, R. Chowdhury, K.J. Courville, M.H. Criqui, D.K. Cundiff, K.C. Dabhadkar, L. Dandona, A. Davis, A. Dayama, S.D. Dharmaratne, E.L. Ding, A.M. Durrani, A. Esteghamati, F. Farzadfar, D.F. Fay, V.L. Feigin, A. Flaxman, M.H. Forouzanfar, A. Goto, M.A. Green, R. Gupta, N. Hafezi-Nejad, G.J. Hankey, H.C. Harewood, R. Havmoeller, S. Hay, L. Hernandez, A. Hussein, B.T. Idrisov, N. Ikeda, F. Islami, E. Jahangir, S.K. Jassal, S.H. Jee, M. Jeffreys, J.B. Jonas, E.K. Kabagambe, S.E. Khalifa, A.P. Kengne, Y.S. Khader, Y.H. Khang, D. Kim, R.W. Kimokoti, J.M. Kinge, Y. Kokubo, S. Kosen, G. Kwan, T. Lai, M. Leinsalu, Y. Li, X. Liang, S. Liu, G. Logroscino, P.A. Lotufo, Y. Lu, J. Ma, N.K. Mainoo, G.A. Mensah, T.R. Merriman, A.H. Mokdad, J. Moschandreas, M. Naghavi, A. Naheed, D. Nand, K.M. Narayan, E.L. Nelson, M. L. Neuhouser, M.I. Nisar, T. Ohkubo, S.O. Oti, A. Pedroza, D. Prabhakaran, N. Roy, U. Sampson, H. Seo, S.G. Sepanlou, K. Shibuya, R. Shiri, I. Shiu, G.M. Singh, J.A. Singh, V. Skirbekk, N.J. Stapelberg, L. Sturua, B.L. Sykes, M. Tobias, B.X. Tran, L. Trasande, H. Toyoshima, S. van de Vijver, T.J. Vasankari, J.L. Veerman, G. Velasquez-Melendez, V.V. Vlassov, S.E. Vollset, T. Vos, C. Wang, X. Wang, E. Weiderpass, A. Werdecker, J.L. Wright, Y.C. Yang, H. Yatsuya, J. Yoon, S.J. Yoon, Y. Zhao, M. Zhou, S. Zhu, A.D. Lopez, C.J. Murray, E. Gakidou, Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **384**(9945), 766–781 (2014)
11. M.G. Schooneman, A. Napolitano, S.M. Houten, G.K. Ambler, P. R. Murgatroyd, S.R. Miller, C.E. Hollak, C.Y. Tan, S. Virtue, A. Vidal-Puig, D.J. Nunez, M.R. Soeters, Assessment of plasma acylcarnitines before and after weight loss in obese subjects. *Arch. Biochem. Biophys.* **606**, 73–80 (2016)
12. S.J. Mihalik, B.H. Goodpaster, D.E. Kelley, D.H. Chace, J. Vockley, F.G. Toledo, J.P. DeLany, Increased levels of plasma acylcarnitines in obesity and type 2 diabetes and identification of a marker of glucolipotoxicity. *Obesity* **18**(9), 1695–1700 (2010)