MCT1 polymorphism among Egyptian children and adolescents as a useful predictor for physical fitness and muscle fatigue.

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Abstract

Background and objectives: Monocarboxylate transporter1 (*MCT1*) is a protein that mediates transport of pyruvate and lactate across cell membranes, its gene contains several polymorphisms (*SNPs*). We aimed to genotype *SNP A1470T* and to study its impact on muscle activity.

Materials and Methods: 108 male children and adolescents were enrolled; 56 patients (easily fatigable after 30 minutes football training) and 52 normal individuals who completed the training protocol without complaint. Both groups were subjected to clinical examination and blood lactate and LDH assay. DNA samples were withdrawn for *MCT1*genotyping using high resolution melt technique.

Results: Overall frequency of TT genotype was highest (44.5%) followed by AT and wild AA genotypes. Genotype AA was significantly lower in patients (OR 1.97) with a statistically higher frequency of allele A among control (56 versus 28 with P<0.001). Significantly higher blood lactate was found in patients. Alleles A and T were in equilibrium among control (56 versus 48, respectively) with marked disequilibrium in patients.

Interpretation and conclusions: Allele A was favorable for *MCT1* function, lactate transport and hence physical fitness. Within patients' groups, AA was not better than AT or TT thus suggesting potential role of training or epigenetic factors in improving allele a expression.

Keywords: *MCT1* A1470T Polymorphism, Lactate, LDH

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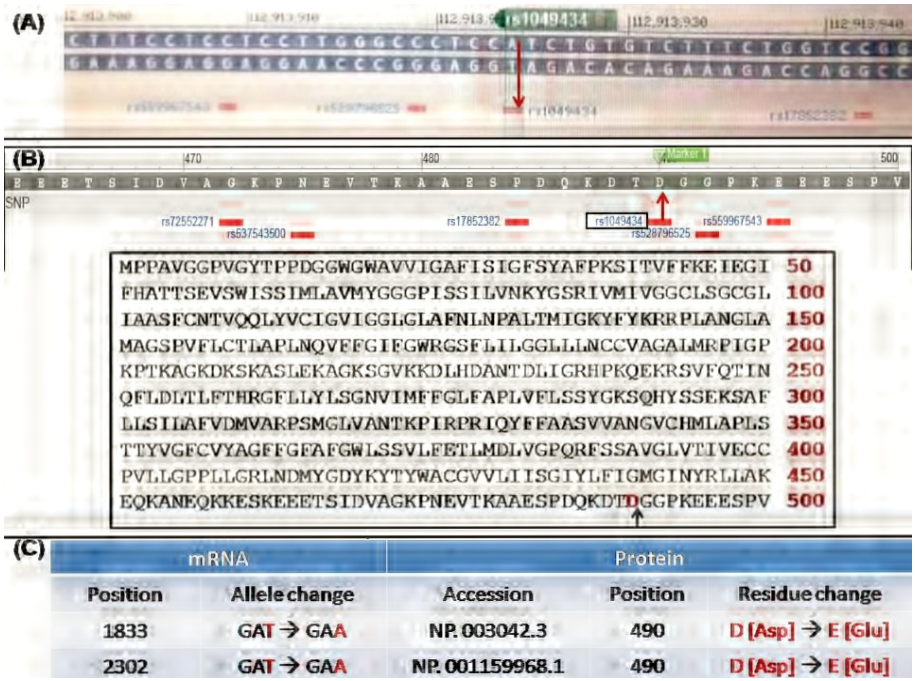
Introduction

Monocarboxylate transporter1 (*MCT1*) is a protein that mediates the transport of pyruvate and lactate across cell membranes of many tissues (OMIM 600682). Lactate is not only an end-product of glycolysis but also an oxidizable substrate; it is produced in glycolytic fibers, oxidized in heart and recycled in hepatic gluconeogenesis [1]. *MCT1* isoform is predominant in the oxidative fibers with high mitochondrial contents, whereas MCT4 is predominant in the glycolytic fibers; *MCT1* and MCT4 facilitate the uptake and extraction of lactate, respectively [2]. On the other hand MCT2 is 60% identical to *MCT1* but they have different distributions; *MCT1* is present mainly in erythrocytes and intestinal cells, however MCT2 is abundant on the surface of hepatocytes. *MCT1* is required for lactate influx to be oxidized in heart and red skeletal muscles that utilize lactate as a major fuel while MCT4 is important for lactic acid efflux after glycolysis and ATP production [3]. In high-intensity exercise, anaerobic metabolism and subsequent lactic acid accumulation necessitate the study of this metabolite and its movements across cell membranes in relation to the training and the genetic polymorphism in its transporter protein; *MCT1* [4].

MCT1 protein is composed of 500 amino acid residues (Figure 1) and encoded by the *MCT1* gene (also known as *SLC16A1*). This gene is mapped on chromosome 1p13.2-p12and contains 5 exons. It spans about 44 kb, the first exon is non-coding, and the first intron is more than 26 kb [5]. The promoter region lacks a TATA box, but it contains potential binding sites for several transcription factors [6]. There is a strong correlation between *MCT1* expression and the oxidative capacity of rat skeletal muscles [7]. Recently, a marked difference in *MCT1* and its ancillary protein CD147 had been detected in the horse skeletal muscles after training [8]. Skeletal muscle activity has a strong influence on the *MCT1* gene expression; muscle inactivity reduces *MCT1* expression [9], however the chronic electrical stimulation increases *MCT1* expression in rats [10]. Moreover, *MCT1* contents in human skeletal muscle have been shown to be elevated after a period of endurance and high-intensity training [11].

The up-regulation of *MCT1* expression in response to increased muscle activity is thought to be based on calcium-dependent protein phosphatase and AMP-activated protein kinase [12]. A great difference in the individual's capacities to transport lactate has been described which is dependent not only on the extent of training but also on their inherent ability [13]. *MCT1* is highly abundant in the central nervous system for lactate transport. High *MCT1*expression has been observed within oligodendroglia and its disruption leads to axonal damage and neuronal loss in animal cell culture models [14].

Mutations in *MCT1 cDNA* were found in patients with rare condition known as cryptic exercise intolerance. Those



Figue 1: *Monocarboxlase tarnsporter 1 (MCT1) gene database as captured from NCBI; (A) Amplified segment of MCT1 gene with the reference sequence of the studied SNP (rs 1049434), inverted red arrow points to the site of SNP, (B) MCT1 protein sequence (last 40 amino acids, above show different sites of SNPs and black rectangle encircles the studied SNP, the whole 500 amino acids, below), upright red and black arrows point to the changed amino acid residue; at codon 490 that causes change of aspartic acid "D" [GAT] to glutamic acid "E" [GAA] , (C) Summary table for the mRNA and its resultant protein residue of the SNP.*

individuals suffered from severe chest pain and muscle cramps on vigorous exercise but otherwise, there were no symptoms [15]. This was explained by the defective lactate efflux that had been linked to a common missense mutation A1470T (rs1049434) in the *MCT1* gene causing codon 490 change (aspartic acid to glutamic acid). Individuals with mutant T allele had lactate transport rates 60-65% less than the mean normal [16] Due to the high frequency of this point mutation in the general population, it is no longer considered as a pathogenic mutation but rather as a SNP being a non-disease causing mutation. Recently, Cupeiro et al examined the influence of the *MCT1* A1470T polymorphism on lactate accumulation after circuit training. Male carriers of T allele of *MCT1* showed higher lactate accumulation than non-carriers during circuit weight training [17,18] Genotyping of *MCT1* A1470T among Russian athletes revealed a significantly higher frequency of a allele and AA genotype in rowers, as well as in the whole cohort of endurance-oriented athletes when compared to the control group. Moreover there was an association between this SNP and the achievement level in male rowers; top-elite and elite male rowers had higher frequencies of A allele and AA genotype than the sub elite rowers, thus suggesting A allele to be considered as a beneficial genetic marker for rowing [19].

There are many disease causing-mutations of *MCT1* gene, most of them are presented by ketoacidosis. Homozygous frameshift mutations in *MCT1* gene causing loss-of-function and hence severe *MCT1* deficiency had been described in a group of patients with severe ketoacidosis [20]. Patients with homozygous *MCT1* mutations described in that study had moderate intellectual disability; whether a direct effect of *MCT1* deficiency in brain or as a result of repeated severe ketoacidosis was still unknown. Although *MCT1* deficiency was prevalent among patients with ketoacidosis, some heterozygous family members and even homozygous mutants did not have any history of ketoacidosis thus suggesting the presence of other factors; genetic or environmental that make this mutation exerted its effects [20].

In the current work, we aimed to genotype the SNP A1470T of *MCT1* gene among Egyptian male children and adolescents and to study its clinical implications on the muscle activity as marked by blood lactate and lactate dehydrogenase (LDH). We will try to explain some clinical phenomena that usually occur in these individuals during their daily life activities e.g. repeated muscle cramps in response to exercises, unexplained easy fatigability and hence refusal of physical share during the school time.

Subjects and Methods

Cohort study involved old children and adolescents (age range 10-15 years) from the Mansoura University Stadium (Dakahlia governorate). Our subjects included two groups: the first group (Patients) comprised 56 individuals who used to have muscle cramps or easy fatigability after 30 minutes of regular football training or escaped the completion of the high intensity protocol. The second group (Control) included 52 individuals who usually completed the high intensity training protocol successfully without any evidence of muscle cramps or injury with matched age with the patient group.

We recorded period of training and optimal timing of blood sampling for biochemical assays at the end of training. All individuals were males; research was done in the gymnasium and the laboratory of physiological measurements in Faculty of

Physical Education, Mansoura University, Egypt in the period from 1, March, 2014 to 1, March, 2016.

All participants were subjected to thorough medical examination before being enrolled into the study. Complete Blood Count, chest x-ray, Electrocardiogram and sometimes echocardiography were done to exclude any factor that could affect the biochemical parameters or lead to poor effort tolerance or even ischemic pain. Written informed consents had been taken from all trainees or their guardians to be enrolled in the study encouraging them that the current work might be the preparatory step for selection of the international players. The Ethical Research Committee (ERC) of Mansoura Faculty of Medicine have reviewed the study design and validated its application.

Biochemical analysis

Blood lactate: It was determined using accusport device (Accutrend Lactate, Boehhringer Mannheim GmbH, Mannheim, Germany) that measures the lactate from a blood spot on strips applying a colorimetric method built in the machine and giving an alarm with the relevant blood lactate level in a method similar to the day-to-day measurement of blood sugar but in a more standardized protocol [21].

LDH activity: LDH was measured at rest and after maximum exertion using spectrophotometry in a 3 ml blood sample. Sample were collected sequentially and stored on ice until the time of analysis. In a mix of NADH and pyruvate at 37 ºC for 1 min, 20 uL of the serum was withdrawn into a covet to be read at 340 nm wavelength. Level of LDH was determined by the rate of formation of NAD that is proportionate to the LDH activity [22]. Two patients developed respiratory distress proved to be due normoglycemic ketoacidosis with marked elevation of the anion gap as shown from the critical blood samples taken during the exercise round.

Study design

All individuals underwent warming for 10 minutes then started running for 5 minutes on a treadmill with synchronous firing of the polar stop watch at a speed 9 km/hr. Heart rates (HR) were counted at the end. All individuals were then given 10 min rest, and after 3 minutes blood samples were withdrawn for lactate measurement. The same steps were repeated 3 times more with increasing speed to 10.8, 12.6 and 14.4 Km/hr successively. Some precautions were taken for all examinee during the study. They included adequate sleep in the day before, no eating 4 hours before testing, any coffee or tea at least 1 hour before the procedure and the 4 steps must be done on the same day taking the results and blood samples by the same assistant. Correlations between exercise time, HR and blood lactate were plotted on a scatter plot (Figure 2).

Molecular analysis of MCT1 polymorphism

A small blood sample (1 ml) was withdrawn from each individual on an EDTA treated test tube for DNA extraction. Molecular study was done using a real-time quantitative PCR (qPCR) with the application of a high resolution melt technique (HRM). A mix of 250 ng/m of DNA, 10 mmol of Tris-HCl and 0.5 mmol of each nucleic acid base and 1 unit of Taq polymerase to a net volume of 40 uL was done. Sequence of primers is deduced from the SNP A1470T of *MCT1* gene indexed in the gene bank of NCBI.

rs1049434 [Homo sapiens]

GGACTTTCCTCCTCCTTGGGCCCTCC **A/T**
TCTGTGTCTTTCTGGTCCGGAGATT

Forwards primer sequence is: TGGCAAAAGAACAGAAAGCAAACGAGC, and reverse primer sequence is: TCCTCCTCCTTGGGCCCTCC. Protocol of amplification included initial heating of the mix to 90 ºC for 15 minutes followed by 40 cycles, denaturation 95 ºC for 20 seconds, annealing 62 ºC for 15 seconds and extension 72 ºC for 30 seconds. Figure 3 showed the analysis results of HRM curve data of qPCR of the *MCT1* polymorphism.

Statistical methods

Data were processed and analyzed using SPSS version 17. Exploration of the quantitative variables revealed violated normality, so median and interquartile were used to describe the central tendency and dispersion. Mann Whitney U test was used to analyze the difference between two genotypes; however Kruskall Wallis U test was used for the analysis of the difference between the three genotypes of each group as regards the quantitative variable (blood lactate and LDH). Hardy Weinberg Equilibrium (HWE) was applied to determine the Odds ratio of each genotype, frequencies of genotypes and alleles within each group taking into consideration the selection bias and the small

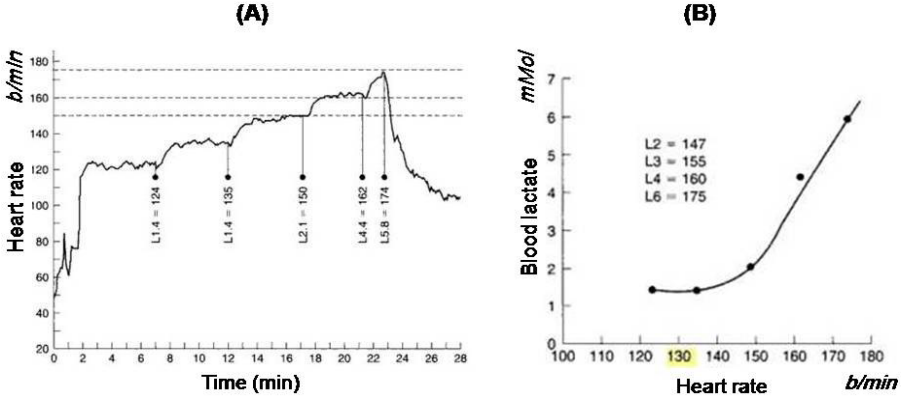
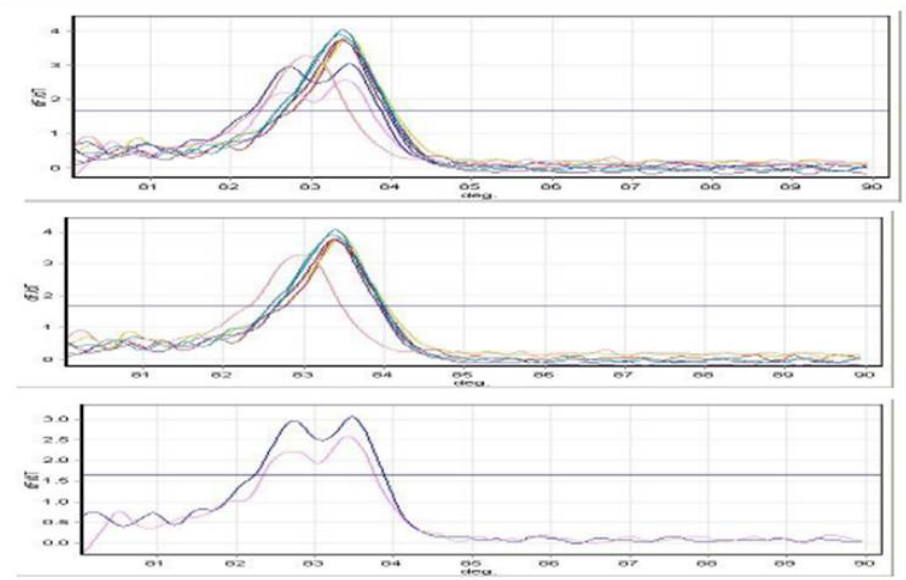


Figure 2: *Scatter plot for the correlation between speed of run and heart rate (A), heart rate and blood lactate level (B).*

sample size. Correlation between blood lactate and LDH was done using Spearman Rank correlation with the scatter plot of all individuals being assigned by their genotypes (Figure 4: note the marked down slope of the best fit line; coefficient (r)=-0.66, with $P<0.001$).

Results

Table 1 showed the three *MCT1* genotypes (the overall frequencies of AA 22.2%, AT 33.3% and TT 44.5%) with quiet different trend in patients and control (14.3, 21.4 and 64.3% in patients versus 30.7, 46.2 and 23.1% in control, respectively). Chi square value was statistically significant (X^2=10.83, P=0.004) which is due to the high odds ratio (OR) for genotype TT (4.91, 95% confidence interval CI=1.7-13.8). Genotype AA frequency is apparently lower in patient compared to control (OR 1.97, CI=0.95-3.8) with a statistically higher frequency of allele A among control (56 versus 28 with P<0.001).



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Peak 1	83.40	83.48	82.73	83.38	82.72	83.35	83.40	82.95	83.45	83.55	83.35
Peak 2			83.48		83.43						

***Figure 3**: Analysis of the high resolution melt (HRM) curve data of quantitative PCR (qPCR) for monocarboxylase transporter 1 (MCT1) gene polymorphism.*

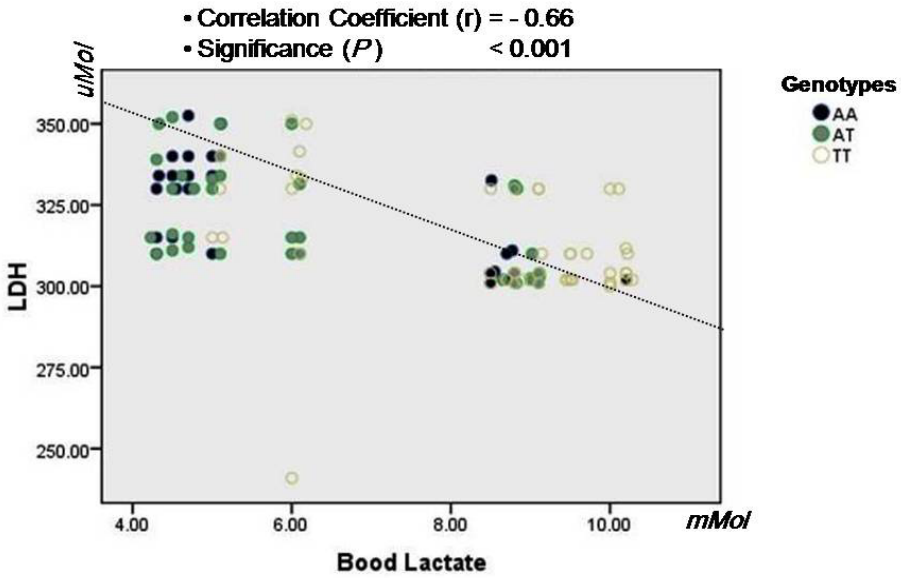

***Figure 4**: Scatter plot for blood lactate and LDH. Individuals are assigned by their A1470T SNP genotypes; black AA, grey AT and white TT. Dotted line represents the best fit line of correlation.*

We tested two blood markers as a measurement of fitness and adaptation against fatigue; blood lactate and LDH activity. There is a statistically negative correlation between blood lactate and LDH (Figure 4). Median Blood lactate values for patients was significantly higher compared to control (9.22, 5.56 respectively, P<0.001); data were not shown in tables. On the other hand, LDH activity at the maximum effort was significantly higher in the control group compared to patients (352 and 298 respectively, P<0.001); data were not shown in tables. Moreover blood lactate in patients with AA genotype was higher than in the control group of the same genotype (P^1=0.003), and similarly in genotypes AT and TT (P^1=0.002, 0.02) respectively (Table 2).

Measurement of blood lactate and LDH activity at the maximum effort in the three genotypes of healthy control showed elevation of blood lactate levels and lowering LDH levels in TT genotype (blood lactate in TT=7.6 versus 4.5 and 4.8 in AA and AT genotypes respectively, P^2=0.003, Table: 2; LDH in TT=315 versus 365 and 330 in AA and AT of the healthy control (P2=0.006) respectively (Table 3). However analysis of the difference in lactate and LDH among the three genotypes of patients did not yield any statistically significant difference (P^2=0.12, 0.22) respectively (Tables 2 and 3). The two patients who developed ketoacidosis were found to be TT genotype.

Applying HWE for the distribution of alleles among patients and control showed that allele A and T were found in equilibrium in control (56 versus 48), yet there was a marked change of the distribution trend (disequilibrium of HWE) among patients with predominance of the mutant allele T (28 versus 84). This disequilibrium makes A/T allele ratio in healthy control (1.2:1.0) to be inverted in the overall population (84: 132, i.e. 1.0:1.6).

Table 1: *Genotyping of MCT1 A1470Tpolymorphism among the two studies groups.*

	Patients (n = 56)	Control (n = 52)	Odds ratio	95% CI
MCT1 AA n (%)	8 (14.3)	16 (30.7)	1.97	0.95-3.82
MCT1 AT n (%)	12 (21.4)	24 (46.2)	0.19	0.07-0.58
MCT1 TT n (%)	36 (64.3)	12 (23.1)	4.91*	1.7-13.8
X^2 = 10.83		P = 0.004*		
Allele A	28	56	1.4	1.1-3.2
Allele T	84	48	1.3	0.95-4.1

Values are number and percentage, P is significant if <0.05.

Table 2: *Blood lactate at maximum exertion among the genotypes of MCT1 A1470Tpolymorphism in the two the studies groups (mMol).*

	Patients Median (I.Q.)	Control Median (I.Q.)	U value	P^1
MCT1 AA	8.5 (6.4 – 9.2)	4.5 (2.3 - 7.8)	14.5	0.003
MCT1 AT	10.3 (8.5 – 11.4)	4.8 (3.5 – 8.9)	15.5	0.002
MCT1 TT	9.2 (8.6 – 10.6)	7.6 (5.5 – 10.2)	8.6	0.02
Z value	4.5	23.2		
P^2	0.12	0.003		

Values are median and interquartiles, P is significant if <0.05, P^1 for difference between the two studied groups regarding each genotype (Mann Whitney U test), P^2 for difference between the three genotypes of each studied group (Kruskal Wallis test).

Table 3: *Lactate dehydrogenase (LDH) at maximum exertion among the genotypes of MCT1 A1470Tpolymorphism in the two the studies groups (uMol).*

	Patients Median (I.Q.)	Control Median (I.Q.)	U value	P^1
MCT1 AA	304 (280 – 312)	365 (352 – 398)	10.5	0.007
MCT1 AT	310 (295 – 330)	330 (325 – 362)	7.5	0.04
MCT1 TT	300 (284 – 318)	315 (285 – 320)	8.1	0.03
Z value	3.14	14.2		
P^2	0.22	0.006		

Values are median and interquartiles, P is significant if <0.05, P^1 for difference between the two studied groups regarding each genotype (Mann Whitney U test), P^2 for difference between the three genotypes of each studied group (Kruskal Wallis test).

Discussion

MCT1 and MCT4 are present in the plasma membranes (sarcolemma) of the skeletal muscles. Sarcolemma MCT expression plays an important role in exercise tolerance. Moreover the ancillary protein CD147 is indispensable for the activity of *MCT1* and *MCT4* [23]. Regulation of MCT expression after acute exercise is a complex process being affected by many other factors like hypoxia, nutritional status and metabolic perturbation that affect the lactate production. In general, exercise produces greater increases in *MCT1* than in MCT4 content. Dissociation between the regulation of MCT content and lactate transport activity has been reported in a number of studies. Changes in MCT content are more common in response to contractile activity, whereas changes in lactate transport capacity typically occur in response to changes in metabolic pathways [24]. Not only *MCT1* but also MCT4 play important roles during maximal exercise in horses; their expression increase 18 weeks after high-intensity training for variable periods especially in MCT4. The precise mechanisms underlying the up-regulation of MCT4 expression are unknown [25].

In the current work, the impact of moderate training exercises on blood lactate and LDH among two cohorts of Egyptian children had been tested. These biochemical changes were correlated with the polymorphism A1470T of *MCT1* gene whose protein function is a lactate transporter. The first report on *MCT1* gene polymorphism and its correlation to muscle fatigue among human was described in a Chinese group of Singaporean population. Authors screened 95 individuals using DNA sequencing to describe any SNPs along *MCT1* (*SLC16A1*) encoding *MCT1* transporter protein [26]. Seven genetic variants were defined of which four were novel; two in the promoter, two in the coding exons, two in the 3' un-translated region and one in a non-coding intron. The 1282G>A (Val428 Ile) is a novel SNP and was found in a heterozygotic state in four subjects. The 1470 T>A (Asp490Glu) was found to be a common polymorphism in that study [26]. In silico prediction of the effects of SNPs on the variant protein was speculative; however the actual role of SNPs should be based on a functional assay.

In the current study, genotyping of the Egyptian children for SNP *MCT1* A1470T (rs1049434) polymorphism had been accomplished using a relatively simpler molecular technique (quantitive PCR; qPCR); among the 216 alleles tested there were 84 A allele and 132 T allele (ratio 1.0:1.6). Applying HWE for the distribution of A/T alleles among patients and control

showed that although alleles A/T were found in equilibrium in the control group (56 versus 48), there was marked predominance of the mutant allele T in patients (84 versus 28). So, allele A could be considered favorable for *MCT1* protein function and lactate transport and hence physical fitness, however factors that make this genetic disequilibrium (small sample size, natural selection and selection bias) should be considered as limitations for this conclusion.

Influence of *MCT1* A1470T polymorphism on lactate accumulation after high intensity circuit training had been investigated in human. Genotype distributions were in equilibrium according to HWE, being 30% wild-type, 50% heterozygous, and 20% homozygous mutant [17], however in our work there was a disequilibrium of HWE; wild AA genotype was present in 22.2%, heterozygous AT in 33.3% and the homozygous mutant TT in 44.5%. Carriers of A1470T polymorphism in *MTC1* gene seem to exhibit a worse lactate transport capability [17]. These data are different from those gained from a mixed male and female moderately active adult Caucasians. In men, AA group had higher lactate values than TT group in all the measures ($p<0.03$) except for the average lactate during the Weight Machine Protocol, in which a borderline significant difference was found ($p=0.07$), however no differences had been observed across genotypes in females. These data suggest an influence of the *MCT1* polymorphism on lactate transport across sarcolemma only in males [18].

MCT1-CD147 complex is the prime lactate transporter in mammalian sarcolemma. In equine red blood cells, activity of the complex and expression of *MCT1* and CD147 are bimodal; high in 70% and low in 30%. Study of the sequence variations and its relation to the bimodal expression of *MCT1* and CD147 had been done. The amounts of *MCT1* and CD147 expressed in RBCs and muscle membranes were measured by Western blot and mRNA levels in muscles by qPCR. *MCT1* were not linked to *MCT1* expression. In CD147, heterozygous SNPs 389A>G (125 Met>Val) and 990C>T (3'-UTR) were associated with low expression of CD147. Also a mutation 168A>G (51 Ile>Val) in CD147 was associated with low *MCT1* and CD147 expression. Low *MCT1* and CD147 mRNA levels in gluteus were associated with low CD147 in RBCs, thus declaring the impact of the polymorphism on CD147 expression but not explaining the bimodality [27]. The bimodal *MCT1* and CD147 expression could be explained by other transcriptional factors beyond the DNA sequence. In our work the difference between patients and control regarding lactate and LDH is related to training and adaptation; moreover the differences within the genotype of each group is in favor of allele A and best with the genotype AA which is significant in the control group($P=0.003$ and 0.006 for lactate and LDH respectively), yet not statistically significant in patients ($P=0.12$ and 0.22 for lactate and LDH respectively). This suggests the role of training or some epigenetic factors in improving the expression of allele A and hence the function of *MCT1* protein as a lactate transporter. This suggestion is supported by the hypothesis that the promoter region contains potential binding sites for several transcription factors [6].

Five patients with symptoms and signs of muscle injury on exercise and heat exposure who showed laboratory evidences of subnormal erythrocyte lactate transport had been investigated for any *MCT1* mutations. One had a missense mutation at a conserved site, two other cases had a different missense mutation at a non-conserved site, and both mutations were found in the heterozygous state but absent in a control of 90 normal individuals. These two mutations may explain the subnormal lactate transport, and hence the muscle injury under environmental stress. The other two cases had lactate transport rates 60-65% of mean normal, but their *MCT1* gene showed a point mutation that had been proved to be a SNP being present in the normal control as well [18]. The lactate transport defect and hence muscle damage in the last two cases with polymorphism could be explained by the presence of other factors that affect *MCT1* expression beyond its DNA sequence i.e. posttranscriptional or epigenetic factors.

As most of *MCT1* mutations reported in literature to cause ketoacidosis are pathogenic [21] the TT genotype of the two patients who had been crashed during exercise in the current study would not be a sufficient explanation, therefore full sequencing of *MCT1* gene is recommended for these two cases. The statistically significant drop of the level of blood lactate noticed in players of both AA and TT genotypes compared to the pre-exercise level could explain the effect of training and exertion of increasing strength on the biochemical improvement of muscle milieu by decreasing metabolic accumulation of lactate resulted from the anaerobic oxidation of glucose [28].

Conclusion

The differences between patients and control in our study were related to the training and adaptation, moreover the differences in biochemical parameters among the genotypes of patients are in favor of allele A and best with the genotype AA, yet statistically insignificant. In other words, within the patient group, genotype AA is not so better than AT or TT, this could suggest the role of training or some epigenetic factors in improving expression of allele A towards lactate transport or LDH consumption.

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