International Journal of Human Movement and Sports Sciences 9(5): 876-883, 2021 http://www.hrpub.org
DOI: 10.13189/saj.2021.090507

The Influence on Mitochondrial Energy (ATP), Lactate-Pyruvate- and Muscularity-Metabolism (CK): Cellular Magnesium Level and Magnesium Supplementation in Elite Sports

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Received May 23, 2021; Revised July 2, 2021; Accepted July 25, 2021

Cite This Paper in the following Citation Styles

(a): *[1] Chanh Thuc Dao , "The Influence on Mitochondrial Energy (ATP), Lactate-Pyruvate- and Muscularity-Metabolism (CK): Cellular Magnesium Level and Magnesium Supplementation in Elite Sports," International Journal of Human Movement and Sports Sciences, Vol. 9, No. 5, pp. 876 - 883, 2021. DOI: 10.13189/saj.2021.090507.*

(b): *Chanh Thuc Dao (2021). The Influence on Mitochondrial Energy (ATP), Lactate-Pyruvate- and Muscularity-Metabolism (CK): Cellular Magnesium Level and Magnesium Supplementation in Elite Sports. International Journal of Human Movement and Sports Sciences, 9(5), 876 - 883. DOI: 10.13189/saj.2021.090507.*

Abstract Muscle injuries and lactate overload during training or at the end of the season, in top team sports, quickly preclude optimal results and participation. Is total magnesium deficiency responsible for these problems in elite athletes and whether magnesium supplementation improves their muscle metabolism or lactate-pyruvate-metabolism? Methods: In 55 elite athletes [male: 25 – female: 30 / soccer: 26 – Olympics: 14 – tennis: 15 – motorsports (DTM-Formula1): whole blood magnesium were determined. In 25 athletes serum and whole blood magnesium, creatine kinase (CK), venous pyruvate and lactate, and the mitochondrial energy level ATP were determined before and after 3 months of daily supplementation with 370mg magnesium and statistically correlated. A Spearman-ranking coefficient of correlation, a chi-quadrat-test by Pearson, and an independent t-test were used with $p<0.05$ this value is reliable, $p<0.01$ highly significant. Results: In 27. 1% of all elite athletes (N=18/55) a whole blood magnesium deficiency (vMg<1.29 mmol/l) was proved. Female athletes were significantly worst supplied than the male athletes [vMg: 1.33 ± 0.11 mmol/l vs. 1.41 ± 0.13 mmol/l ($p<0.024$].Whole blood magnesium (1.31 ± 0.15 mmol/l before vs 1.45 ± 0.09 mmol/l after therapy, $p<0.00025$), serum magnesium (0.78 ± 0.06 mmol/l before vs 0.93 ± 0.05 mmol/l after therapy, $p<0.00025$), the venous pyruvate (0.21 ± 0.12 mg/dl before vs 0.39 ± 0.10 mg/dl after therapy, $p<0.00025$) and mitochondrial ATP (90.56 ± 10.11 %T cells before vs 99.07 ± 1.21 %T cells after therapy, $p<0.00025$) significantly increased after 3 months supplementation of 370mg magnesiumoxide. Venouslactate (10.62 ± 3.50 mg/dl vs. 8.08 ± 2.09 mg/dl after therapy, $p<0.0025$), the pyruvate lactate ratio (69.98 ± 52.81 vs. 22.93 ± 12.29 after therapy, $p<0.00025$) and the creatine kinase CK (501 ± 323 U/l before vs. 294 ± 161 U/l after therapy, $p=0.018$) significantly reduced under 3-months old daily magnesium substitution. For each 0.1 mmol/l increase in whole blood magnesium, the pyruvate improves significantly by 0,06 mg/dl and the pyruvate lactate ratio decreases significantly by 90.9. The improvement of the pyruvate as well as the pyruvate lactate ratio leads to a significant improvement in muscularity metabolism (CK) [increase by 0.1 mg/dl pyruvate decreases CK by 89.39, $p=0.018$, reduction of lactate pyruvate ratio decreases CK by 25.45, $p=0.008$). An absolute risk reduction of 68% (18/25 before vs 1/25 after therapy) could be calculated for muscular injuries. No side influences were reported. Conclusion: The determination of serum magnesium in elite sports is not meaningful.

Whole blood magnesium (vMg), on the other hand, plays a significant role in the prevention of muscularity injuries, independently of the type of sports, by optimizing pyruvate lactate metabolism and thus mitochondrial energy production ATP. Further treatment studies have to prove if optimizing whole blood magnesium can lead to an increase in performance.

Keywords Influence, Mitochondrial, Energy (ATP), Lactate-Pyruvate, Muscularity-Metabolism

1. Introduction

Micronutrients including vitamins and trace elements are essential. To maintain all the physiological energy of the body on a daily basis, they need to interact with each other [1]. Extensive training with frequent high lactic acidosis, a tight playing schedule, unbalanced or improper diet, frequent travel, and high psychological stress lead to extensive consumption of these micronutrients, resulting in injury in 12.9% of cases and therefore to training absences and competition cancellations [3]. Magnesium is the fourth most abundant mineral in our body and essential for humans. It plays a critical role in health and performance in athletes. Intracellular magnesium energy is a cofactor in over 300 enzyme systems regulating protein synthesis and energy production (Table 1) [7]. In addition, it plays an important role in immune defense, oxidative stress regeneration, and pain modulation [9].

Table 1. Systems regulating protein synthesis and energy production

Protein synthesis:	Creatine kinase (CK)
	Protein kinase
	Protein cyclase
Energy metabolism (protein-fat)	Propionyl-CoA carboxylase
Energy metabolism (carbohydrate) aerobic:	Hexokinase
	Phosphofructokinase
	Pyruvate kinase
	Pyruvate Dehydrogenase (PDH)
Energy metabolism (carbohydrate) anaerobic:	Lactate Dehydrogenase (LDH)
	Pyruvate Decarboxylase
Mitochondrial metabolism:	Mg-ATP complex V
	Na+/K*-ATPase
	Ca++-ATPase
	H+-ATPase
	Pyruvate dehydrogenase (PDH)

Therefore, an optimal magnesium status is crucial for constant training and performance (optimal bone-muscularity-immune metabolism) in elite athletes. Magnesium is also responsible for maintaining normal muscularity contraction and relaxation [11]; optimal magnesium intake can significantly improve this muscularity energy in athletes [12]. Dietary magnesium controls the conversion of 25 (OH)D3 to its active form, which supports calcium influx and thus bone metabolism. Magnesium deficiency thus correlates negatively with bone metabolism by decreasing osteoblast and increasing osteoclast activity [13]. Decreased magnesium intake (below 400mg in men and below 310mg in women per day) is associated with lower bone density, which counts as a risk factor for stress fractures in competitive athletes [16]. In addition, intense anaerobic training or competition leads to increased magnesium loss in sweat and urine, resulting in magnesium deficits in up to 40% of cases [8]. Targeted correction of proven magnesium deficiencies is significantly associated with increased muscular performance and improved cardio-vascular energy in athletes [12].

However, determination of the blood magnesium status is a challenge, because the serum levels of magnesium do not reflect the current intracellular magnesium supply, since only 1% of the body magnesium circulates in the serum, but 50% of the body magnesium is stored in the bone and 49% intracellularly in the muscularity and tissue [23]. The determination of magnesium in whole blood is the most meaningful method to determine the exact magnesium status due to the consideration of the intracellular magnesium content and thus to reliably indicate cellular deficits [25]. The aim of this study is to evaluate the blood magnesium status of top athletes of various sports and in an observational study to correlate the changes in whole blood or serum magnesium status under magnesium supplementation with its impact on mitochondrial and muscularity metabolism.

Methods: 55 top athletes exercising different sports (team sports: soccer - individual sports: athletics, tennis, motor sports) were included in this study. All participants gave their written consent for data collection. Zellular magnesium in whole blood was examined in all 55 athletes. In addition, 25 elite athletes were substituted with 370µg magnesium oxide daily for 3 months in an observational study. Serum magnesium, whole blood magnesium, creatine kinase, venous lactate and pyruvate, and cellular ATP were determined before and after supplementation and calculated in relation to the symptom muscularity injury. Using a questionnaire, the frequency of medically confirmed muscularity-tendon injuries (muscularity-fiber as well as muscularity-bundle tears and tendon-muscularity tears) was assessed in these 25 competitive athletes.

Magnesium (serum) = sMg

Magnesium in serum was determined using an Abbott Alinity C automated laboratory instrument according to the manufacturer's instructions (order no. 8P1920).

Whole blood magnesium (Na-heparin blood) = vMg

Magnesium in whole blood was determined by atomic

absorption spectrometry (AAS) after acid digestion.

CK (Serum)

Creatine kinase in serum was determined using an Abbott Alinity C automated laboratory analyzer according to manufacturer's instructions (Order No. 8P4220).

Mitochondrial Energy by Mitochondrial Membrane Potential (ATP Level)

Peripheral blood mononuclear cells (PBMC) fraction was isolated from heparinized blood by Ficoll density gradient centrifugation and recorded at a concentration of 1million PBMCs/ml in RPMI medium containing 5% serum. Measurements were performed using the Cell Meter™ JC-10 Mitochondrial Membrane Potential Assay Kit optimized for flow cytometry from ATT Bioquest (Catalog number: 22801) according to the manufacturer's instructions on a FACS Calibur from Becton Dickinson. The dye JC-10, derived and optimized from JC-1, binds selectively in the mitochondrial membrane and changes its fluorescence spectrum from orange to green with decreasing membrane potential. The membrane potential can be considered as a direct summation marker and endpoint for ATP production. As read out, the percentage of T cells (CD3+) without reduction of membrane potential was recorded ("ATP level").

Venous Pyruvate and Lactate

Lactate was determined from NaF blood using an Abbott Alinity C automated laboratory device according to manufacturer's instructions (order no. 8P2120). Pyruvate was also determined photometrically from NaF blood using a quantitative enzymatic UV kit from Greiner Diagnostic GmbH according to the manufacturer's instructions (order no. 180000). The quotient is calculated from both measured values by dividing the lactate value by the pyruvate value.

2. Statistical Analysis

Data were statistically analyzed using IBM®SPSS® software 25. To calculate the correlations between the different parameters, the Pearson correlation coefficient (rP) was used for samples with $n \geq 40$ and no contradiction to the normal distribution in the Kolmogroff-Smirnoff test ($P>0.1$). If the conditions were violated, the Spearman correlation coefficient (rSP) was applied. For 2-group mean comparisons, a Levene test was performed to test for variance homogeneity, followed by an independent T test for homogeneous ($P>0.1$) or inhomogeneous variances with two-sided questioning. Results were considered significant for $p \leq 0.05$ and highly significant for $p \leq 0.01$.

3. Results

Table 2 shows the characteristics of the 55 study participants [male: 25 - female: 30 / soccer: 26, of which Olympic athletes: 14 - tennis: 15 - motor sports (DTM Formula1): [4]. Serum magnesium deficiency was not detected in any athlete, but whole blood magnesium deficiency (<1.29 mmol/l) was detected in 27.1% of cases (N=18/55). Female athletes were highly significantly worse supplied with whole blood magnesium (1.33 ± 0.11 vs. 1.41 ± 0.13 mmol/l, $p<0.024$) than their male counterparts. The best supply of whole blood magnesium (1.54 ± 0.11 mmol/l) was shown by the motor athletes.

Daily administration of 370mg magnesium oxide (185mg each in the morning and evening) resulted in a highly significant increase in serum magnesium (0.78 ± 0.06 mmol/l before therapy vs 0.93 ± 0.05 mmol/l after therapy, $p<0.0002$), whole blood magnesium (1.31 ± 0.15 mmol/l before therapy vs 1, 45 ± 0.09 mmol/l after therapy, $p<0.00025$), venous plasma pyruvate (0.21 ± 0.12 mg/dl before therapy vs 0.33 ± 0.10 mg/dl after therapy, $p<0.00025$) and cellular ATP (90.6 ± 10.1 %T cells before therapy vs 99.1 ± 1.2 %T cells after therapy, $p<0.00025$) [Figure 1], as well as to a highly significant decrease in venous plasma lactate (10.62 ± 3.50 mg/dl before therapy vs 8.06 ± 2.09 mg/dl after therapy, $p<0.001$), of lactate-pyruvate quotient (70 ± 53 before therapy vs 23 ± 12 after therapy, $p<0.00025$) and creatine kinase (CK) (457.38 ± 316.06 U/l before therapy vs 304.50 ± 168.56 U/l after therapy, $p<0.036$) [Tab. 3]. Among these, an absolute risk reduction of 68% (18/25 before therapy vs 1/25 after therapy) could be calculated for muscularity injuries. No side influences (osmotic diarrhea) were complained.

Table 2. Whole blood magnesium (vMg) in gender and sports (N=55)

	Total(N=55)	Female (N=30)	Male (N=25)	Soccer (N=26)	Tennis (N=14)	Motor-sport (N=15)
vMg (1.29-1.69 mMol/l)	1.37± 0.15	1.33*± 0.11	1.41* ± 0.13	1.38 ± 0.15	1.33 ± 0.06	1.54 ± 0.11

* $p<0.024$

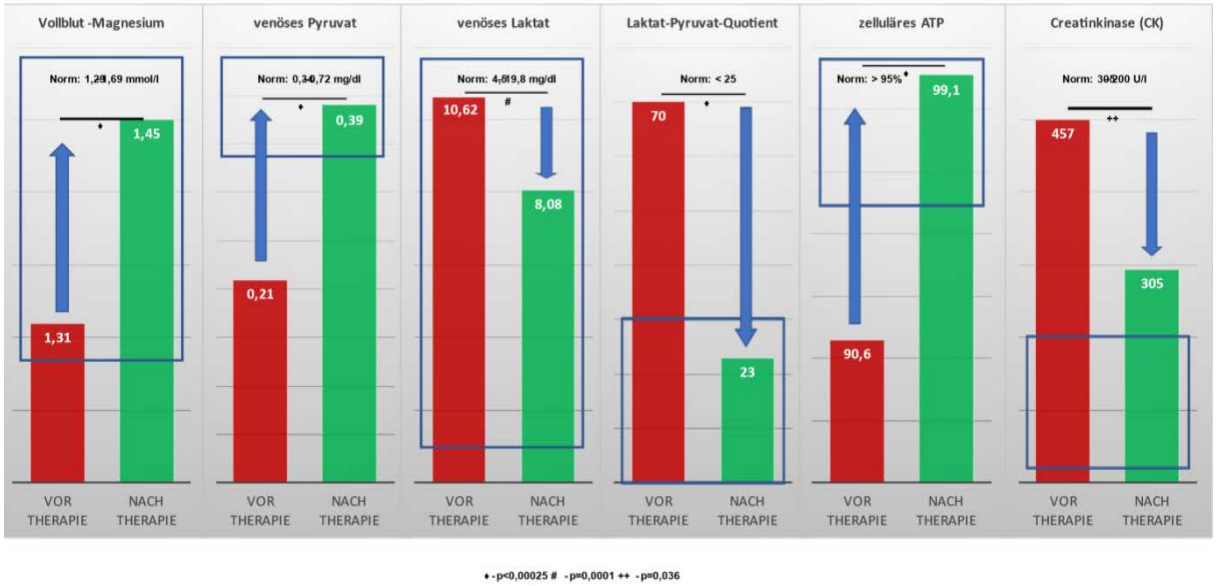

Figure 1. Values before and after 3 months of supplementation with 370 mg magnesium oxide

Table 3. Values before and after 3 months of supplementation with 370 mg magnesium oxide

	Serum-Magnesium (sMg) 0.66 – 1.07 mmol/l (n=16)	Whole Blood Magnesium (vMg) 1.29 – 1.69 mmol/l (n=25)	Pyruvate 0.34-0.72 mg/dl (n=25)	Lactate 4.5-19.8 mg/dl (n=25)	Lactate-pyruvate quotient < 25 (n=25)	ATP 95-100%T-Zellen (n=25)	CK 30 -200 U/l (n=8)
pre-therapy	0.78± 0.06	1.31± 0.15	0.21± 0.12	10.62± 3.50	70± 53	90.6± 10.1	457.38±316.06
post-therapy	0.93± 0.05	1.45± 0.09	0.39± 0.10	8.08± 2.09	23± 12	99.1± 1.2	304.50± 168.56
Significance	p<0.00025	p<0.00025	p<0.00025	p=0.001	p<0.00025	p<0.00025	p=0.036

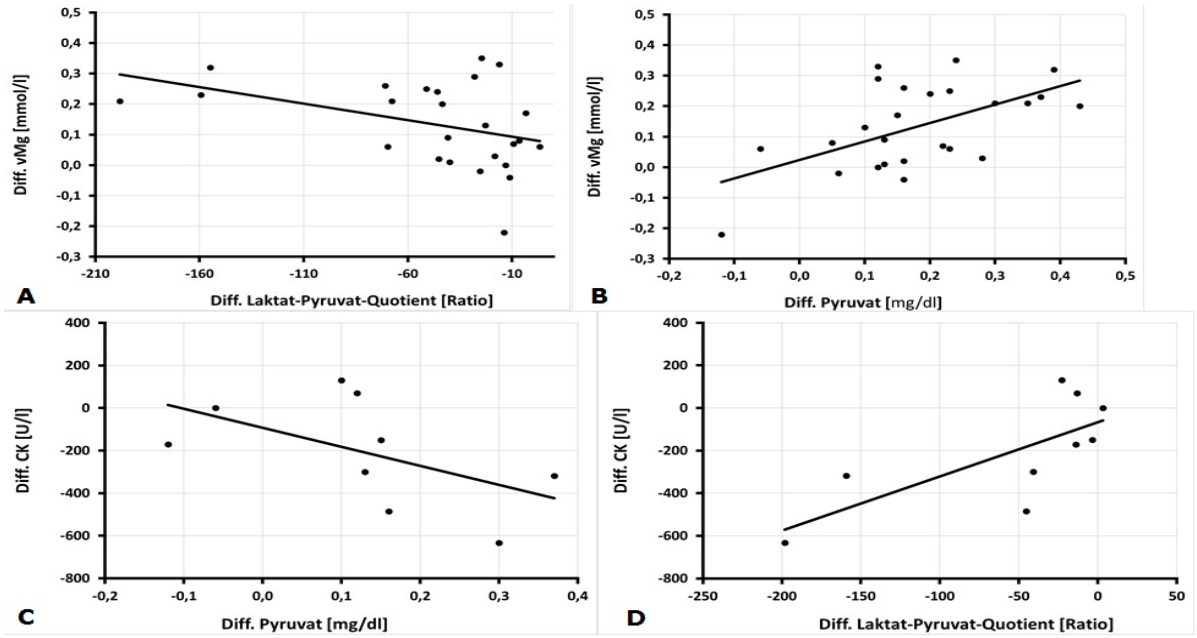

Figure 2. A: Relationship between the change in lactate-pyruvate ratio [ratio] after 3 months of magnesium supplementation and the change in whole blood magnesium [mmol/l] in 25 athletes, (rSP = 0.443, y = -0.0011x + 0.0823 - p = 0.013); B: Relationship between the change in pyruvate [mg/dl] after 3 months of magnesium supplementation and the change in whole blood magnesium [mmol/l] in 25 athletes*, (rSP = 0.414, y = 0.604x + 0.024 - p = 0.02). C: Relationship between the change in pyruvate [mg/dl] after 3 months of magnesium supplementation and creatine kinase (CK) [U/l] in 9 athletes*, (rSP = 0.700, y = -893.94x - 91.997 - p = 0.018); D: Zusammenhang zwischen der Veränderung desLaktat-Pyruvat-Quotienten [ratio] nach 3-monatiger Magnesiumsubstitution und der Creatinkinase (CK) [U/l] bei 9 Sportler* Innen, (r_{SP} = 0,767,y = 2,5452x –66,684 – p = 0,008)

The athlete, who experienced a muscularity-tendon injury after 3 months despite daily magnesium supplementation, tore the anterior cruciate ligament without external influence.

As well as a highly significant decrease of the lactate-pyruvate quotient (per increase of vMg by 0.1 mmol/l a decrease of the lactate-pyruvate quotient by 90.9 p=0.013) [Fig.2A].

The significant improvement of whole blood magnesium by daily magnesium supplementation over 3 months resulted in a highly significant increase of pyruvate. Per increase of vMg by 0.1 mmol/l a significant increase of pyruvate by 0.06 mg/dl (p=0.02) was calculated [Fig.2B]

This significant improvement of pyruvate (per increase of pyruvate by 0.1 mg/dl) calculates a decrease of CK by 89.39 U/l, p=0.018 [Fig.2C]. At the same time, the lactate-pyruvate quotient decreases. With the decrease of the lactate-pyruvate quotient by 10, a highly significant decrease of creatine kinase by 25.45 U/l (p=0.008) is observed simultaneously [Fig.2D]. Despite highly significant improvement of serum magnesium under daily magnesium supplementation for 3 months, no correlation to mitochondrial parameters (pyruvate, lactate, cellular ATP) or muscularity metabolism parameter (creatine kinase) could be detected.

The results show that in elite athletes, regardless of the sport, whole blood magnesium (vMg) deficiency (< 1.29 mmol/l) is detectable in 27.1% of cases and finds confirmation by Pollock et al [26] [22% of 192 athletes had vMg deficiency]. The average vMg level of the athletes in our study of 1.37 ± 0.15 mmol/l is also confirmed in the literature as 1.30 - 1.34 mmol/l [23]: 1.30 ± 0.16 mmol/l (N=41), Pollock et al. (26): 1.34 ± 0.14 mmol/l (N=192), [27]: 1.31 ± 0.39 mmol/l (N=114)], whereas in our study female athletes are significantly worse supplied with vMg than male athletes (1.33 ± 0.11 mmol/l vs 1.41 ± 0.13 mmol/l, p=0.024). This is also confirmed by the study of Pollock et al [26] [female 1.33 ± 0.06 mmol/l vs male 1.38 ± 0.04 mmol/l, p<0.05]. In this study [26], athletes with muscularity tendon injury vs athletes without muscularity tendon injury history have significantly worse vMg levels (1.31 ± 0.07 mmol/l vs 1.35 ± 0.05 mmol/l, p<0.05). Na et al. (28) and Srebro et al. [29] demonstrated that magnesium as an antagonist of the NMDA receptor plays an important role in the development of chronic pain as magnesium deficiency leads to amplification and upregulation of NMDA signaling and thus to tendon-muscularity pain in athletes [30].

Also in our therapeutic study, the mean vMg level of the athletes was 1.31 ± 0.15 mmol/l, with vMg deficiency (< 1.29 mmol/l) detected in 40% of the athletes (10/25). Serum magnesium level (sMg) was within the normal range in all participants (0.78 ± 0.06 mmol/l), and no athlete was found to be sMg deficient (< 0.66 mmol/l). Also in the literature, no sMg deficiency could be detected in any athlete so far: the average sMg level in the studies was between 0.81-0.84 mmol/l [Fogelholm (27): 0.81 ± 0.05 mmol/l (N=114), Molina-Lopez (31): 0.83 ± 0.06 mmol/l (N=14), Scheidtweiler (36): 0.84 ± 0.04 mmol/l (N=18)]. In our 25 competitive athletes, daily supplementation of 370mg magnesium oxide significantly increased both sMg and vMg levels (Fig.1 or Tab.2), but only the increase in vMg level resulted in a significant change in glucose utilization (pyruvate and lactate) and muscularity metabolism (creatine kinase) [Fig.2B-D).

4. Discussion

In our substitution study, an average improvement of 0.1 mol/l vMg resulted in a significant improvement of pyruvate synthesis by 0.06 mg/dl (Fig.2B), which simultaneously led to a significant decrease in tissue acidification (measured in lactate-pyruvate quotient) by 90.9 units (Fig.2A). Comparable results were observed by Cinar et al (32) who were able to achieve significantly better lactate clearance compared to the control group (N=30, p<0.05) when magnesium was substituted for 4 weeks (10mg/kgKG/day). Setaro et al (22) demonstrated in their randomized control trial (N=52) daily magnesium substitution (350 mg/d-1/4 weeks vs. 500mg maltodextrin/d-1/4 weeks) not only a significant increase in vMg level but also a significant decrease in lactate production and a concomitant improvement in muscularity performance (counter movement jumps).

Further placebo-controlled therapy studies with daily substitution of 100 - 350 mg magnesium for 4 - 12 weeks show the same, significant influences (reduction of lactate production, faster recovery and increased muscularity strength and training performance) [31,33]. Also in our therapy study, daily substitution of 370mg magnesium oxide via improvement of glucose utilization resulted in a significant improvement of muscularity metabolism (CK) [Fig.2C-D] and above that also performance (Fig.3C: significant improvement of velocity at the 4mmol lactate limit of 0.68 m/s per 0.1mmol/l magnesium in whole blood above the lower normal limit of 1.29 mmol/l, p=0.0024) [35]. For every 0.1 mg/dl increase in the pyruvate level under magnesium substitution, a significant reduction in creatine kinase (CK) of 89.39 U/l can be achieved; when tissue acidity, measured by the lactate-pyruvate quotient, is relieved by 10 units, the CK level even drops highly significantly by 25.45 U/l (Fig.2C-D). Comparable studies are not available in the international literature. The significant improvement in glucose utilization in pyruvate appears to be due to the improved kinetics of the magnesium-dependent intracellular enzymes hexokinase and phosphofructokinase [Fig.#B-①+②], smuggeling into the mitochondrion for oxidative phosphorylation via

magnesium-dependent pyruvate dehydrogenase (Fig.4-PDH) and converted to energy (ATP) via magnesium-dependent mitochondrial ATPases [Fig.3B-④ - ⑤ - ⑥]. Proteins and lipids can also be intramitochondrially converted to energy ATP via enhancement of magnesium-dependent carbonyltransferases and propionyl-CoA carboxylase [Fig.4], respectively, or used in the citrate cycle for protein synthesis. The significant improvement in vMg level under daily magnesium supplementation for 3 months significantly optimizes glucose utilization to pyruvate, significantly increases mitochondrial ATP production, and leads to a significant decrease in CK via muscularity lactate unloading (significant decrease in lactate-pyruvate quotient), thus optimizing muscularity metabolism (Fig.3A), which leads to an improvement in performance (Fig.3C) and is shown in our study to result in an absolute risk reduction in muscularity-tendon injuries of 68%.

5. Conclusions

Elite athletes are marginally supplied with magnesium in blood serum, but deficiently with whole blood magnesium. Women experience a significantly lower level of vMg than male athletes. Further placebo-controlled randomized studies to a longer period of at least one competition season must show whether these significant magnesium-dependent intracellular and mitochondrial parameter changes lead to a sustainable prevention of muscular injuries and an increase in performance in strength and endurance.

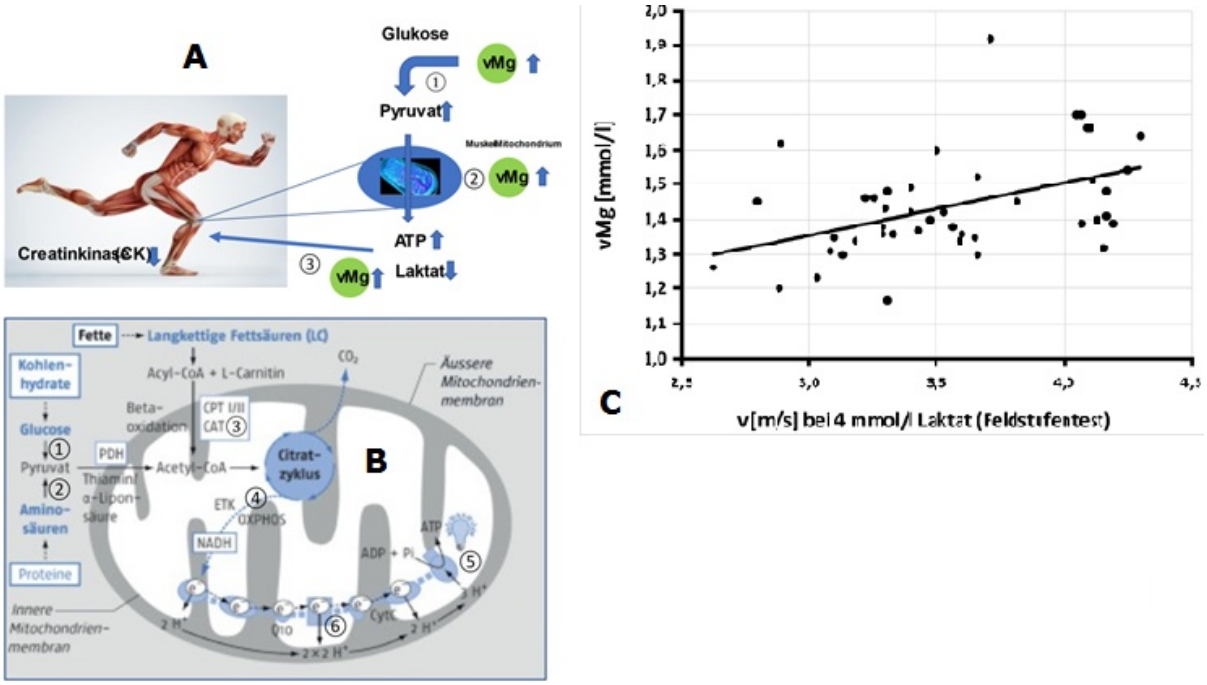

Figure 3. A: Procedure of mitochondrial glucose metabolism: optimization of muscularity metabolism (CK) by increasing whole blood magnesium level (vMg). ① = Magnesium-dependent hexokinase and phosphofructokinase, ② = Magnesium-dependent Na+/K+-ATPase with Mg-ATP complex V, ③ = Magnesium-dependent ADP kinase; B: Magnesium-dependent mitochondrial conversion of food energy into cellular energy (ATP). PDH = pyruvate dehydrogenase ① hexokinase-phosphofructokinase-pyruvate kinase ② protein kinases-protein cyclases ③ carbonyltransferase-propionyl-CoA carboxylase ④ oxidative phosphorylation ⑤ Mg-ATP complex with Na+/K+ATPase ⑥ H+ or Ca++ATPase (from: Gröber U. MedPharm Scientific Publishers, Stuttgart, 2009 [34] modified after Erpenbach et al.); C: Relationship between speed [m/s] at 4 mmol/l lactate in the field level test and magnesium in whole blood [mmol/l] in 44 field hockey players, (rP = 0.446, y = 0.1469x + 0.9147 - p = 0.0024) [35];

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