

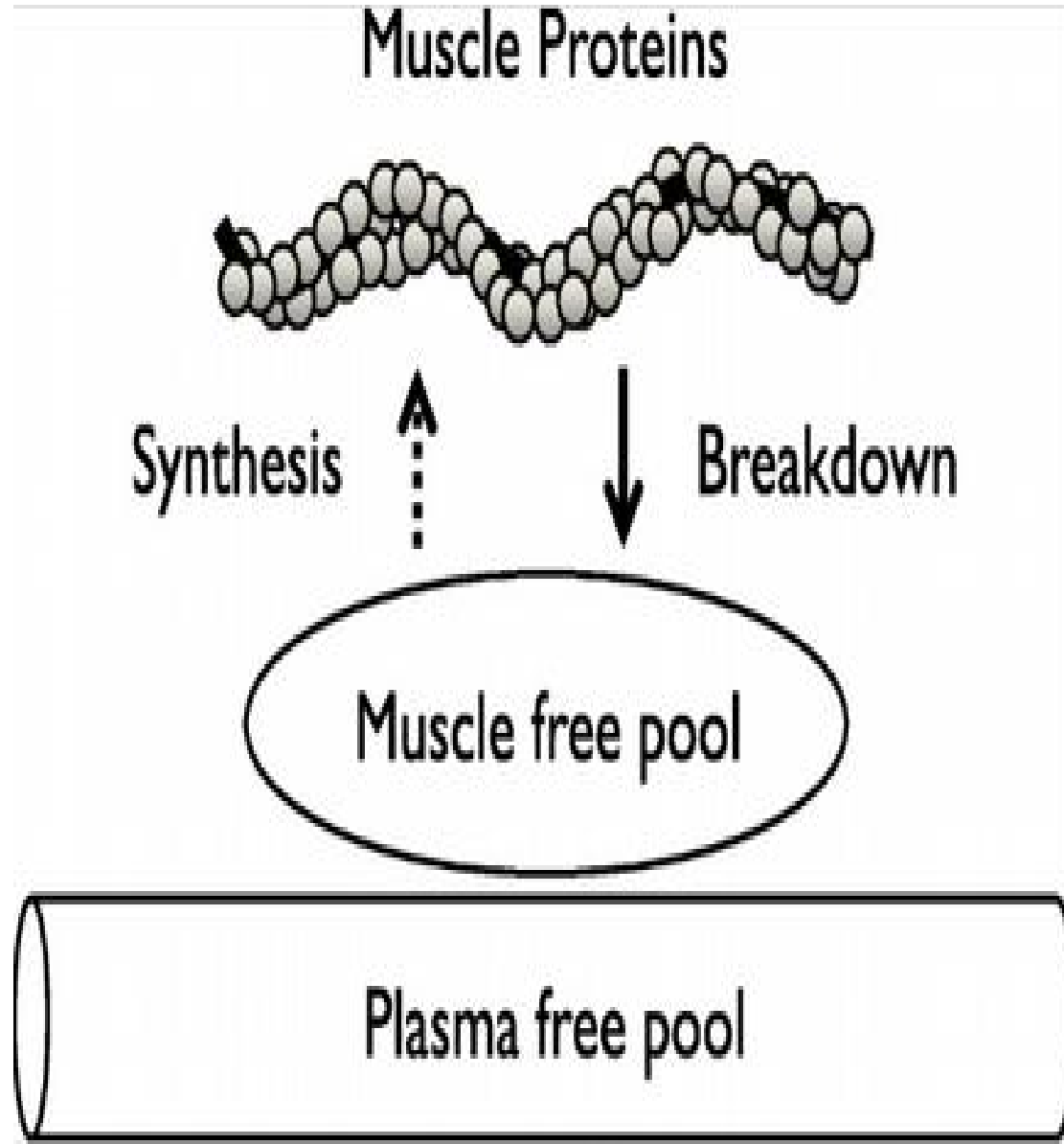
Hydroxymetylbutyrát



Marcela Káňová
Colours of sepsis 2019

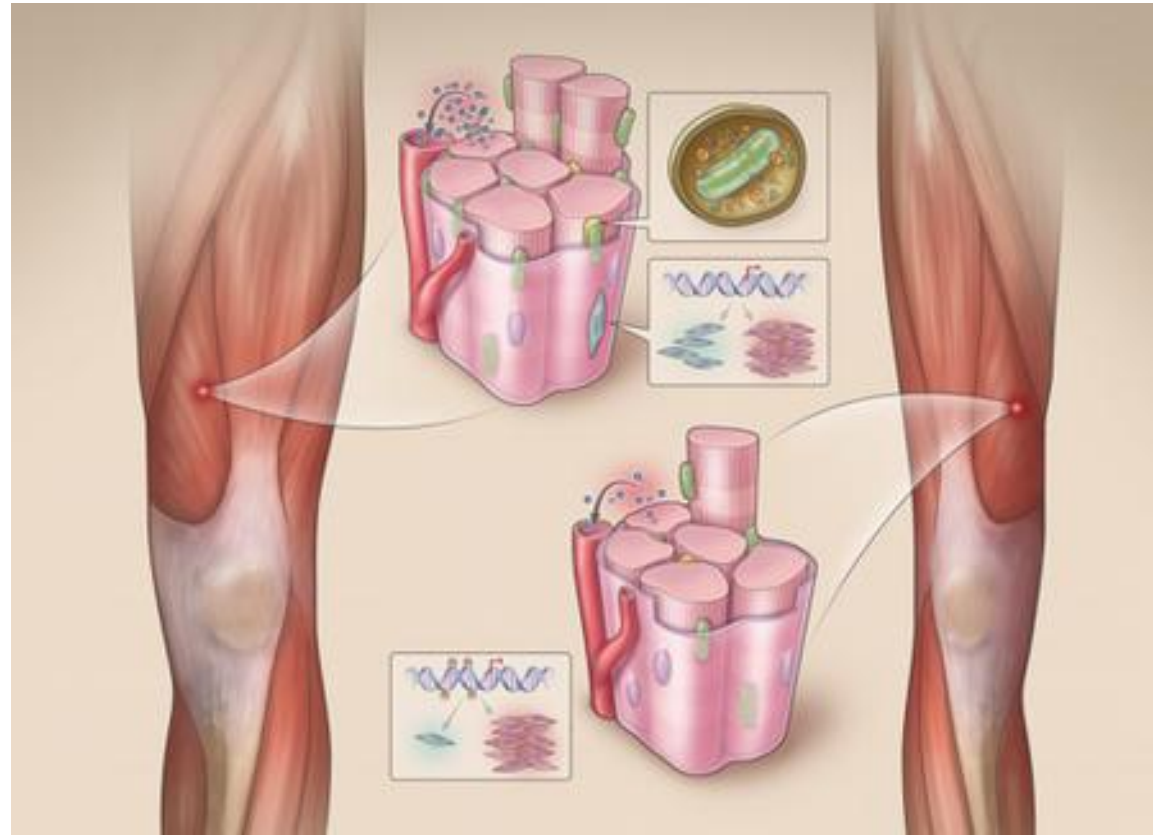
Sarcopenie

- Healthy ageing (WHO): the process of developing and maintaining the functional ability that enables wellbeing in older age.
- Sarcopenia-ztráty svaloviny a funkce s věkem
- Od 40-50 let pokles cca o 8% za dekádu
- *protein turnover*:



Sarcopenie

- Pokles postprandiální MPS
- Digesce a absorpce proteinů
- Redukce nutritivního flow (inzulin, capillary recruitment)
- Redukce anabolických signálních kaskád (rapamycin, mTOR)



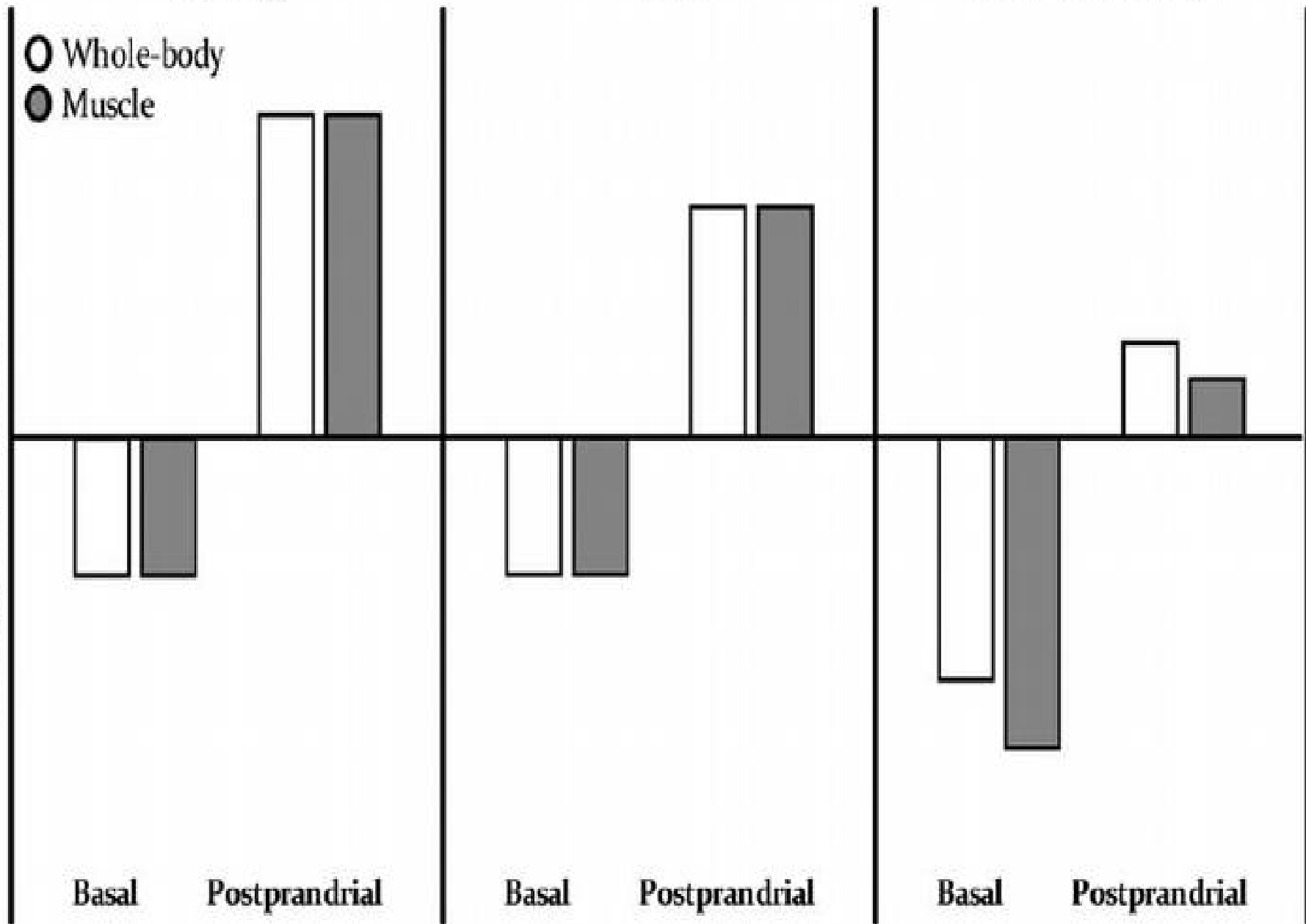
Young

Old

Critical Illness

- Whole-body
- Muscle

Net protein balance



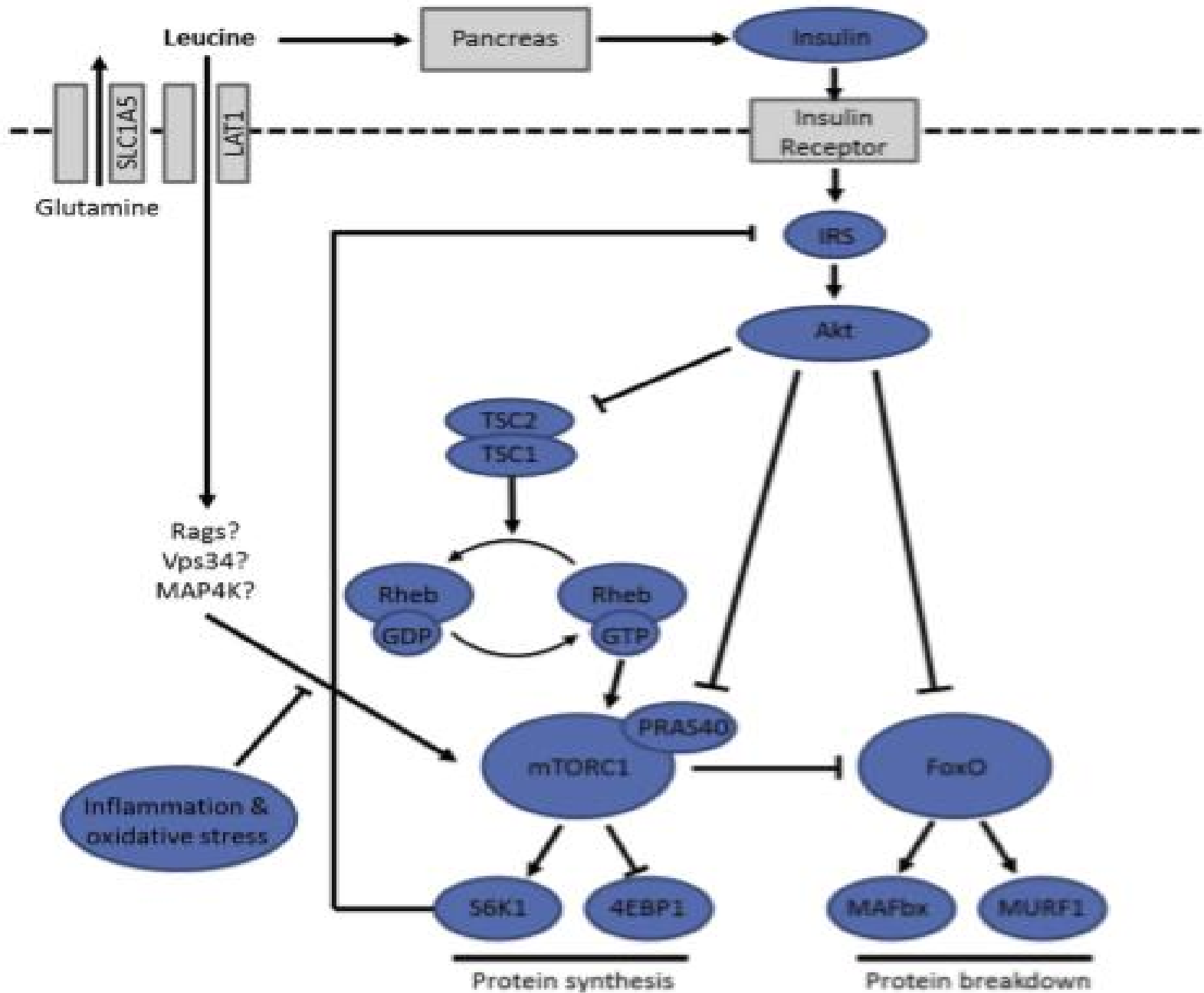
Anabolická rezistence kriticky nemocných

- **Věk**: chybí stimulace MPS (AMK) po jídle, i.v.
- Horší sensitivita anabolických signálů (mTOR)
- **Inzulinorezistence**- netlumí se MPB
- **Imobilita**- pokles MPS již za týden po imobilizaci
- klesá **nutritivní flow** (inzulinem mediovaná vazodilatace, snížená citlivost GLUT4)
- **Stresový metabolismus**- katabolické hormony, cytokiny- nárůst MPB
- **Zánět**

Hydroxymethylbutyrate HMB

- Metabolit ess AMK leucinu
- Anabolický efekt ve stimulaci proteosyntézy
- Antikatabolický efekt leu v tlumení MPB ve vysokých hladinách (10mM/l)- za tento efekt je odpovědný metabolit leu HMB
- Nissen et al 1996: suplementace HMB tlumí MPB, zrychluje regeneraci svalů po zátěži (trénink), zvyšuje sval sílu, LBM (u zdravých)
- Suplementace dále u pacientů s tumorózní kachexií, stařecké sarcopenie, po imobilizaci
- U kriticky nemocných pacientů – nejednotné výsledky studií, vliv na svalovou sílu, LBM

Anabolické kaskády



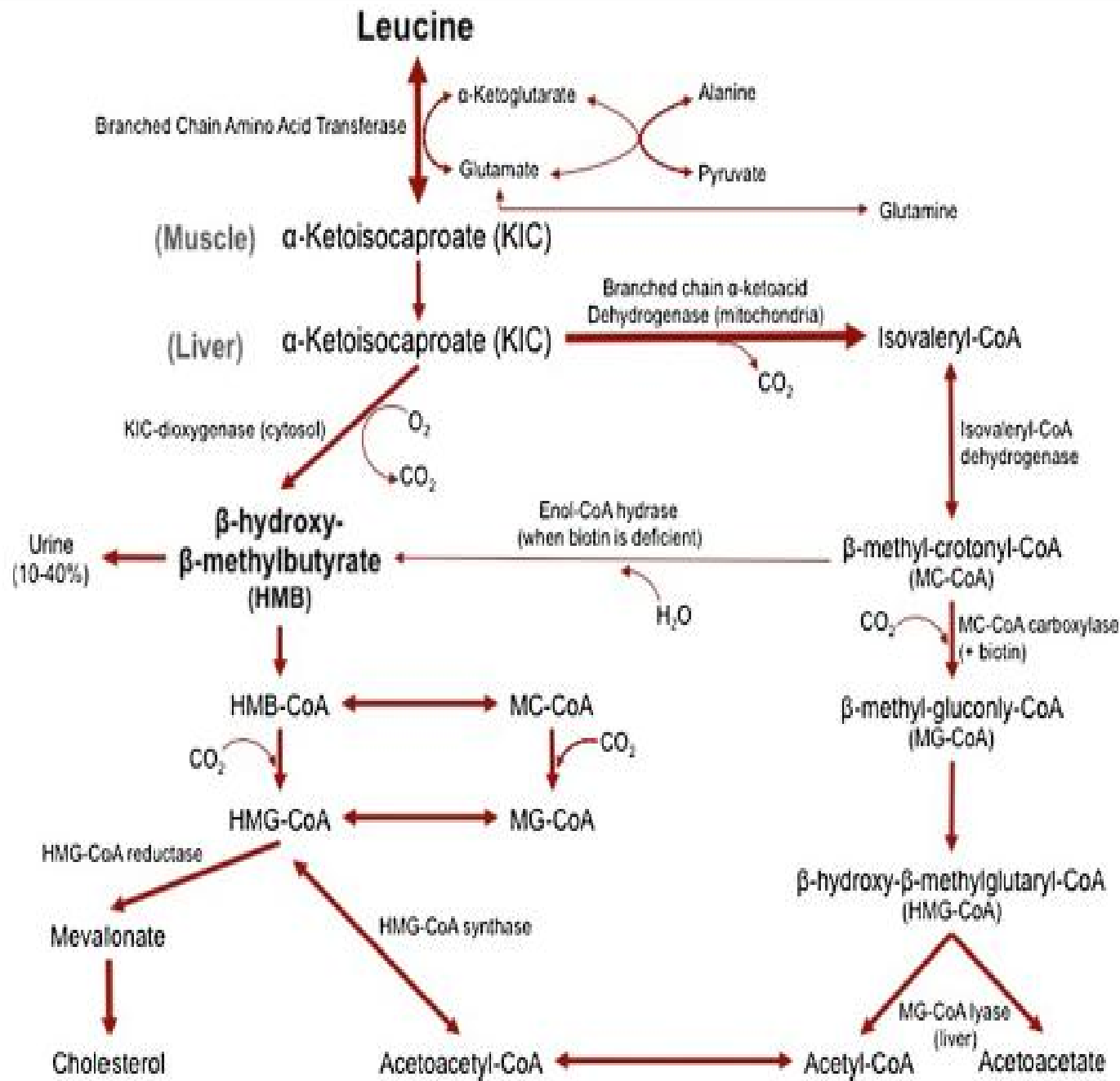
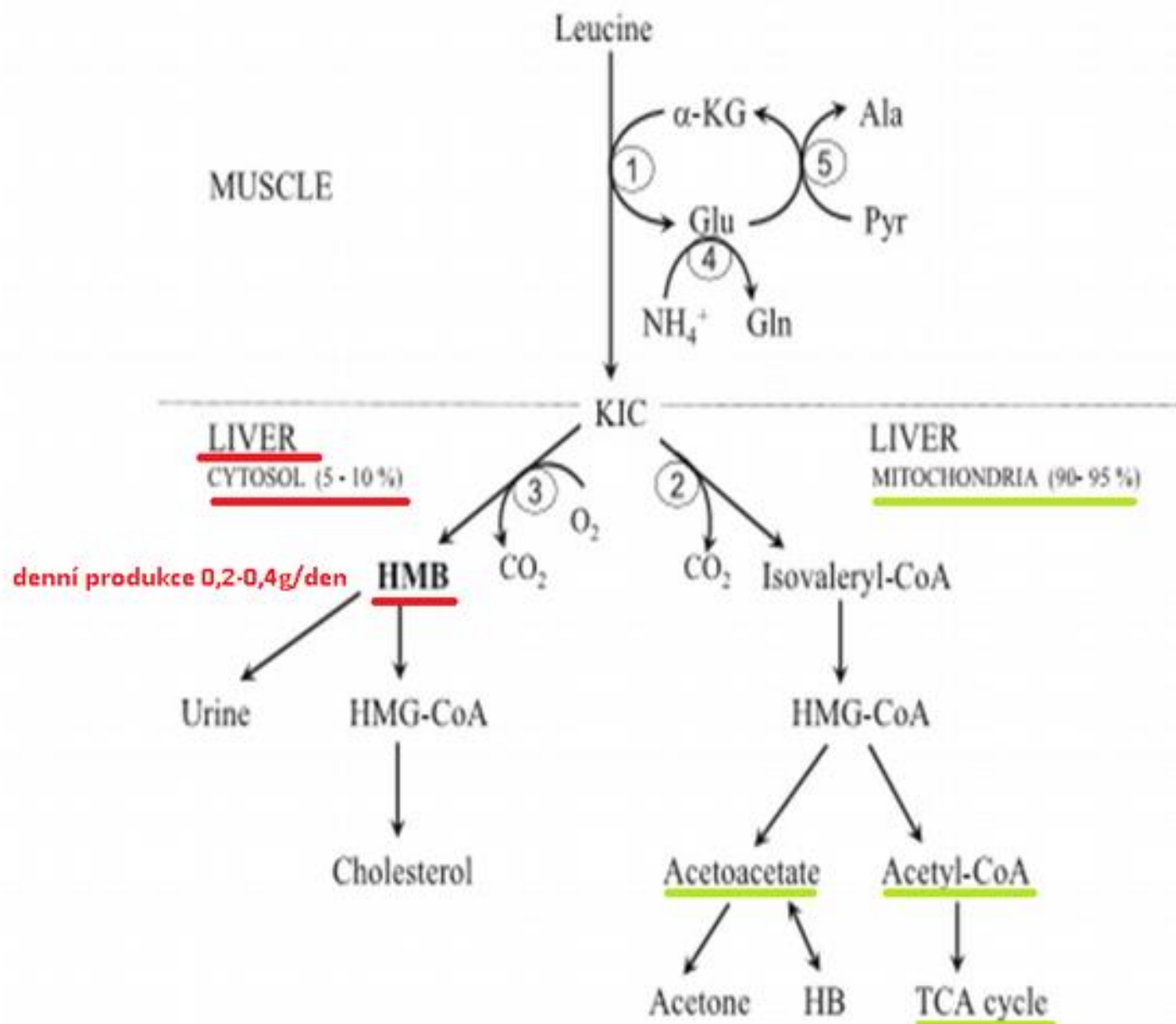
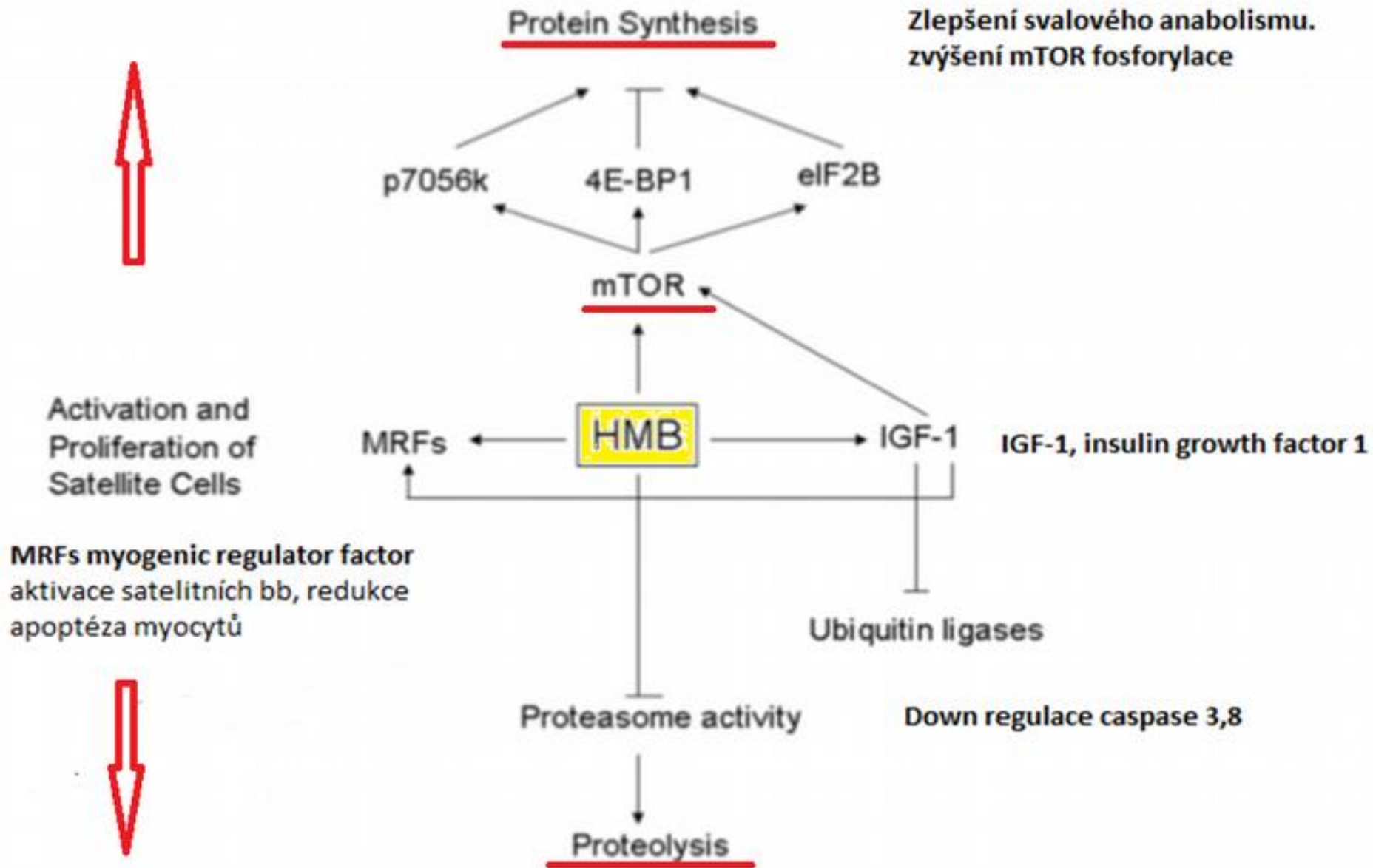


Figure 1 The metabolism of beta-hydroxy-beta-methyl-butyrate.

Figure 1 Pathways of HMB synthesis and catabolism HMB, beta-hydroxy-beta-methylbutyrate; KIC, alpha-ketoisocaproic acid; HB, beta-hydroxybutyrate; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-CoA. 1, BCAA aminotransferase; 2, BCKA dehydrogenase; 3, KIC dioxygenase; 4, glutamine synthetase; 5, alanine aminotransferase.



HMB- stimulace proteosyntézy, blokování proteolýzy

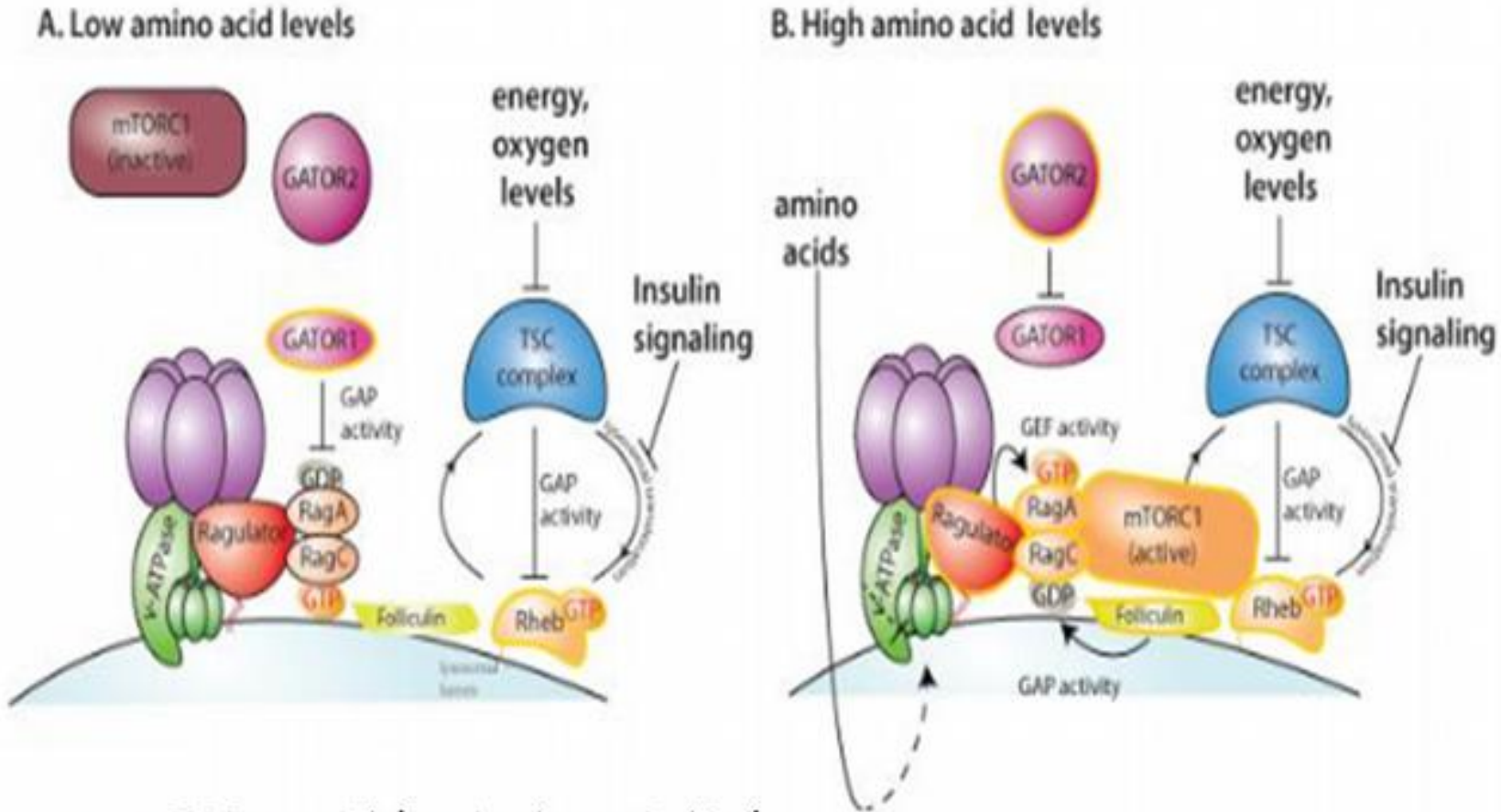
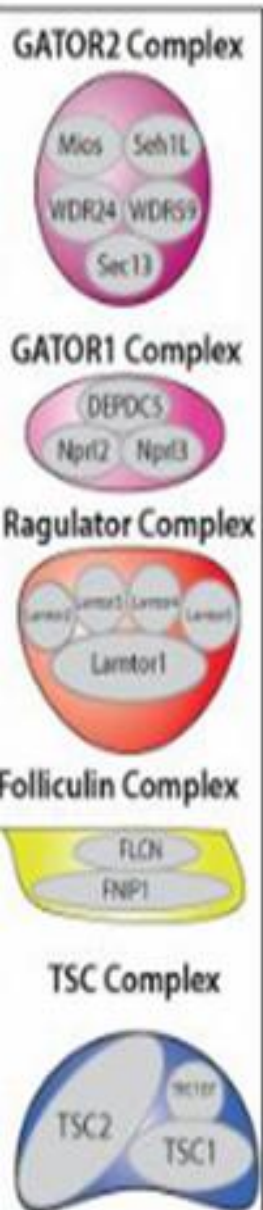


Regulace mTORC1 AMK, rapamycinový komplex

- Mnohobob organismus- signální kaskády - **crosstalk**
- Rapamycinový komplex mTORC1 : hlavní regulační kaskáda **růstu, anabolismu**
- **Stimulátorem AMK: LEU/HMB, ARG + vit D**
- Translokace mTOR z cytozolu na povrch lysosomu
- mRNA translace, **proteosyntéza**

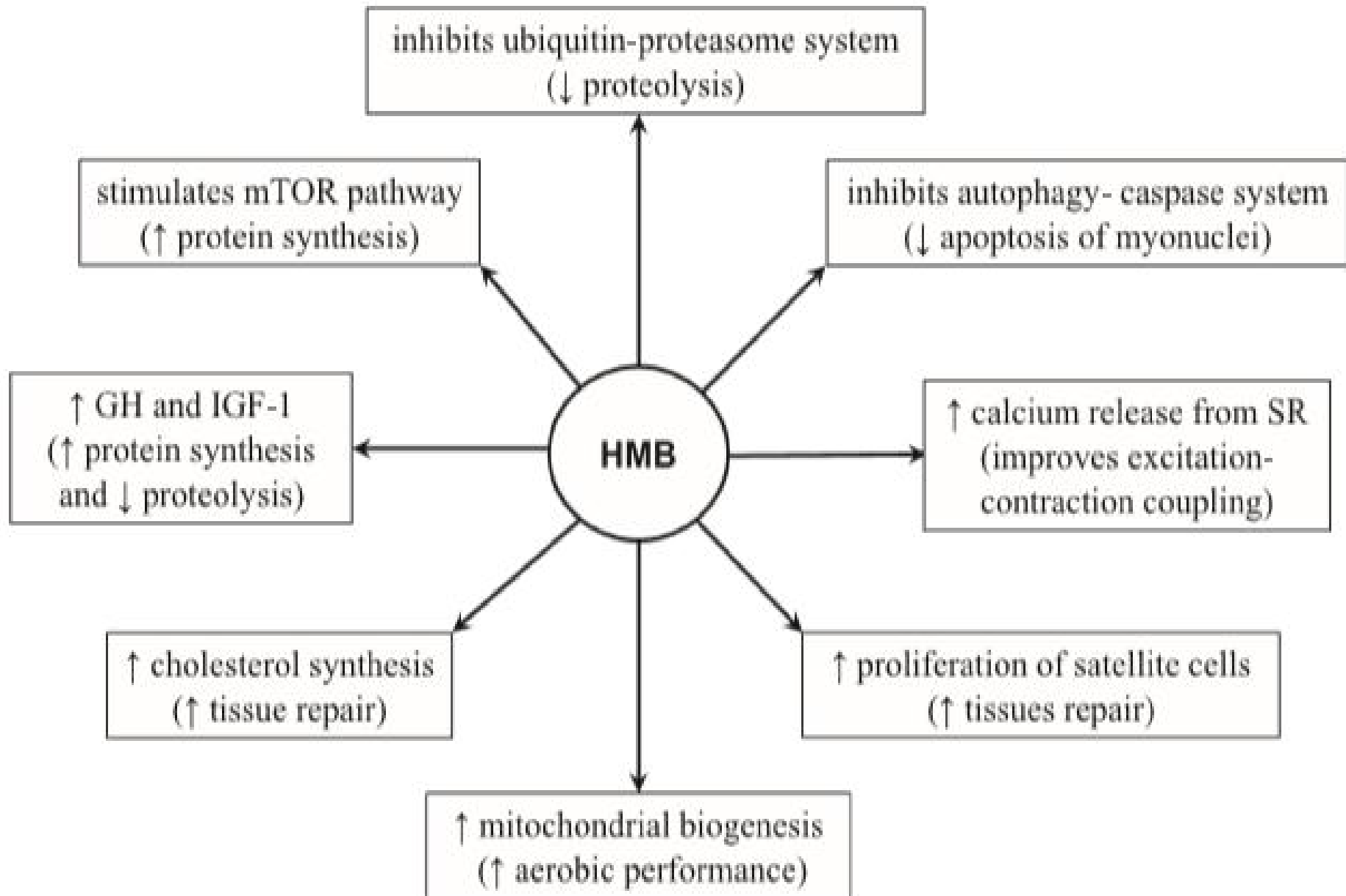


mTORC1 signální kaskáda, stimulace AMK



- mTOR atypická serin-threonin kináza
- TORC2-proliferace bb
- TORC1 (raptor, deptor...)růst, anabolický program RNAtanslace
- represe autofagie, inhibice kaspáz

Mechanismus pozitivního vlivu HMB na svalovinu



REVIEW

Open Access

International Society of Sports Nutrition Position Stand: beta-hydroxy-beta-methylbutyrate (HMB)

Jacob M Wilson^{1*}, Peter J Fitschen², Bill Campbell^{3†}, Gabriel J Wilson⁴, Nelo Zanchi^{5†}, Lem Taylor^{6†}, Colin Wilborn^{6†}, Douglas S Kalman⁷, Jeffrey R Stout⁸, Jay R Hoffman⁸, Tim N Ziegenfuss⁹, Hector L Lopez^{9,10}, Richard B Kreider¹¹, Abbie E Smith-Ryan¹² and Jose Antonio^{13†}

- 1. zkrátí zotavovací fázi (trénování i netrénování)
- 2. zlepší svalovou sílu, výdrž, aerobní metabolismus
- 3. 38mg/kg/den 3g/den
- 4. zvýší LBM, redukuje FM
- 5. chron podávání je bezpečné

Suplementace HMB u mladých, trénink

- HMB zesiluje svalovou sílu, snižuje tréninkem podmíněné svalové trauma, urychluje regeneraci, snižuje vyčerpání
- Větší výsledky u netrénovaných jedinců (HMB redukuje MPB po cvičení, mechanické trauma- zánět)
- U trénovaných (opakovaný trénink redukuje MPB), efekt 14 dní před navýšením fyzické aktivity, maximalizace zátěže



Studie- benefit HMB na LBM při cvičení 18 studií

Study design	Benefits	Reference
Untrained individuals, HMB (1.5 or 3 g/day), resistance training for 3 or 7 weeks	↑ muscle mass and strength, ↓ muscle damage	Nissen <i>et al.</i> ⁸
Untrained men, HMB (3 or 6 g/day), resistance training for 8 weeks	↑ muscle mass and strength, ↓ muscle damage	Gallagher <i>et al.</i> ²⁹
Untrained individuals, HMB (3 g/day), resistance training for 8 weeks	↑ muscle mass and strength, ↓ muscle damage	Jowko <i>et al.</i> ³⁰
Recreationally resistance-trained men, HMB (3 g) before lower body resistance exercise	Combination of HMB and cold water immersion after exercise improved performance recovery	Gonzalez <i>et al.</i> ³¹
Strength-trained and power-trained individuals, HMB (3 g/day) and ATP (400 mg/day), resistance training for 8 weeks	↑ LBM and strength	Lowery <i>et al.</i> ³²
Volleyball players, HMB (3 g/day) for 7 weeks	↑ muscle mass and strength, ↑ anaerobic performance	Portal <i>et al.</i> ³³
Non-resistance-trained men, amino acid-based formula containing HMB, heavy resistance training for 12 weeks	↑ muscle mass and strength, ↓ muscle damage	Kraemer <i>et al.</i> ³⁴
Non-resistance-trained men, HMB (3 g/day) + KIC (0.3 g/day) for 14 days prior to a single bout of heavy resistance exercise	↓ muscle damage	Van Someren <i>et al.</i> ³⁵
Volunteers running at least 48 km/week, HMB (3 g/day) for 6 weeks prior to a prolonged run (20 km)	↓ muscle damage	Knitter <i>et al.</i> ³⁶
Cyclists, HMB (3 g/day) for 2 weeks	↑ aerobic performance	Vukovich and Dreifort ³⁷
Recreationally active subjects, HMB (3 g/day), ergometer tests over a 4 week period	↑ aerobic performance	Robinson <i>et al.</i> ³⁸
Active college students, HMB (3 g/day), exercise for 5 weeks	↑ aerobic performance	Lamboley <i>et al.</i> ³⁹
Rowers, HMB (3 g/day) for 12 weeks	↑ LBM and aerobic performance	Durkalec-Michalski and Jeszka ⁴⁰
Athletes practicing wrestling, judo, jiu-jitsu, karate or rowing; HMB (3 g/day) for 12 weeks	↑ LBM and aerobic performance	Durkalec-Michalski and Jeszka ⁴¹
Trained and untrained individuals, HMB (3 g/day), resistance training for 4 weeks	↑ LBM and muscle strength regardless of gender and training status.	Panton <i>et al.</i> ⁴²
Resistance-trained men, HMB (3 g/day), resistance training for 12 weeks	↑ LBM and muscle strength	Wilson <i>et al.</i> ⁴³
Resistance-trained men, HMB (3 g) before high-volume resistance exercise	↓ muscle damage and improved recovery	Wilson <i>et al.</i> ⁴⁴
Untrained individuals, HMB (3 g/day), high intensity training for 4 weeks	↑ physical working capacity	Miramonti <i>et al.</i> ⁴⁵

Studie neprokazující benefit HMB při cvičení 9 studií

Study design	Result	Reference
Non-resistance-trained subjects, HMB (40 mg/kg /day) for 6 days before maximal isokinetic exercise of elbow flexors	No beneficial effect on muscle soreness, arm girth, and torque measures	Paddon-Jones et al. ⁴⁷
Resistance-trained men, HMB (0.3 or 6 g/day), resistance training for 28 days	No beneficial effect on muscle strength and body composition	Kreider et al. ⁴⁸
Rugby players, HMB (3 g/day) for 6 weeks	No beneficial effect on aerobic and anaerobic ability	O'Connor and Crowe ⁴⁹
Rugby players, HMB (3 g/day) for 6 weeks	No beneficial effect on muscle strength and endurance	O'Connor and Crowe ⁵⁰
Resistance-trained athletes, HMB (3 g/day) for 6 weeks	No beneficial effect on muscle strength, body composition, and markers of muscle damage	Slater et al. ⁵¹
Football players, HMB (3 g/day) for 4 weeks	No beneficial effect on muscle strength and body composition	Ransone et al. ⁵²
Resistance-trained subjects, HMB (3 g/day) for 9 weeks	No beneficial effect on body composition	Thomson et al. ⁵³
Football players, HMB (3 g/day) for 10 days	No beneficial effect on anaerobic power and creatine kinase and myoglobin in blood	Hoffman et al. ⁵⁴
Recreational exercisers, HMB (3 g/day) + KIC (0.3 g/day) for 11 days before downhill running	No benefits on indices of muscle damage	Nunan et al. ⁵⁵

Efekt HMB u starých pacientů



- **Vzestup LBM po cvičení**
 - ✓ *Vukovič*: 3g/den > 70let + cvičení
- Vzestup LBM, pokles fat mass, vzestup síly
 - ✓ *Flakoll*: zlepšení get-up and go testu
 - ✓ *Baier*: kombinace HMB/ARG/LYS/vitD, vzestup LBM
 - ✓ *Luis*: HMB (1,5g) + vit D (12ug), vzestup LBM
 - ✓ *Cramer*: 20/14g prot + 499/147 D3, 1,5g HMB
- Malnutriční, sarcopeničtí senioři- zlepšení
 - ✓ *Deutz*: staří (kardiální selhávání, pneumonie, CHOPN...) pokles mortality, zlepšen nutriční stav
 - ✓ *Deutz*. Staří ležící- prevence poklesu LBM

Efekt HMB u starých pacientů 13 studií

Study design	Effects of HMB	Reference
Animal studies		
Rats, 20 months of age, HMB and β -alanine supplementation (equivalent to human doses of 3 and 2.4 g per day, respectively) for 8 weeks	No significant effect on muscle mass, force or fatigability; \downarrow expression of MuRF1	Russ et al. ⁶¹
Mice, 19 months of age, HMB (514 mg/kg) or β -alanine (411 mg/kg) supplementation for 8 weeks	\downarrow decline in muscle function	Vallejo et al. ²¹
Rats, 34 months of age, hindlimb suspension for 2 weeks and reload for 2 weeks, HMB (340 mg/kg/day) orally	\downarrow fibre area (in plantaris and soleus muscles)	Hao et al. ¹⁷
Rats, 34 months of age, hindlimb suspension for 2 weeks and reload for 2 weeks, HMB (340 mg/kg/day) orally for 35 days	\uparrow muscle mass, fibre cross-sectional area and proliferation of stem cells during the reloading period	Alway et al. ⁶²
Human studies		
HMB/Arg/Lys mixture (2 g/5 g/1.5 g per day) for 1 year	\uparrow lean tissue mass and protein turnover	Baier et al. ⁶³
Bed-ridden subjects, HMB (2 g/day) for 2 or 4 weeks	\downarrow urinary urea nitrogen excretion	Hsieh et al. ⁶⁴
HMB (3 g/day) and exercise for 8 weeks	\uparrow body fat loss	Vukovich et al. ⁶⁵
HMB/Arg/Lys mixture (2/5/1.5 g per day) for 12 weeks	\uparrow limb circumference, leg and handgrip strength;	Flakoll et al. ⁶⁶
	\uparrow whole body protein synthesis	
HMB/Arg/Lys mixture (2/5/1.5 g per day) for 1 year	\uparrow muscle mass, \uparrow muscle strength only when vitamin D status was adequate	Fuller et al. ⁶⁷
HMB/Arg/Gln mixture for 2 weeks	\uparrow collagen synthesis in muscle	Williams et al. ⁶⁸
HMB (1.5 g/day) + mild fitness programme for 8 weeks	\uparrow muscle strength, \uparrow physical performance parameters	Berton et al. ⁶⁹
HMB (3 g/day), bed rest for 10 days followed by resistance training for 8 weeks	HMB supplementation preserves muscle mass during bed rest	Deutz et al. ⁷⁰
HMB (3 g/day) for 24 weeks, both exercise and non-exercise groups	\uparrow muscle strength, no difference between exercising and non-exercising groups	Stout et al. ⁷¹

HMB efekt u kriticky nemocných - muscle wasting chorob 13 studií

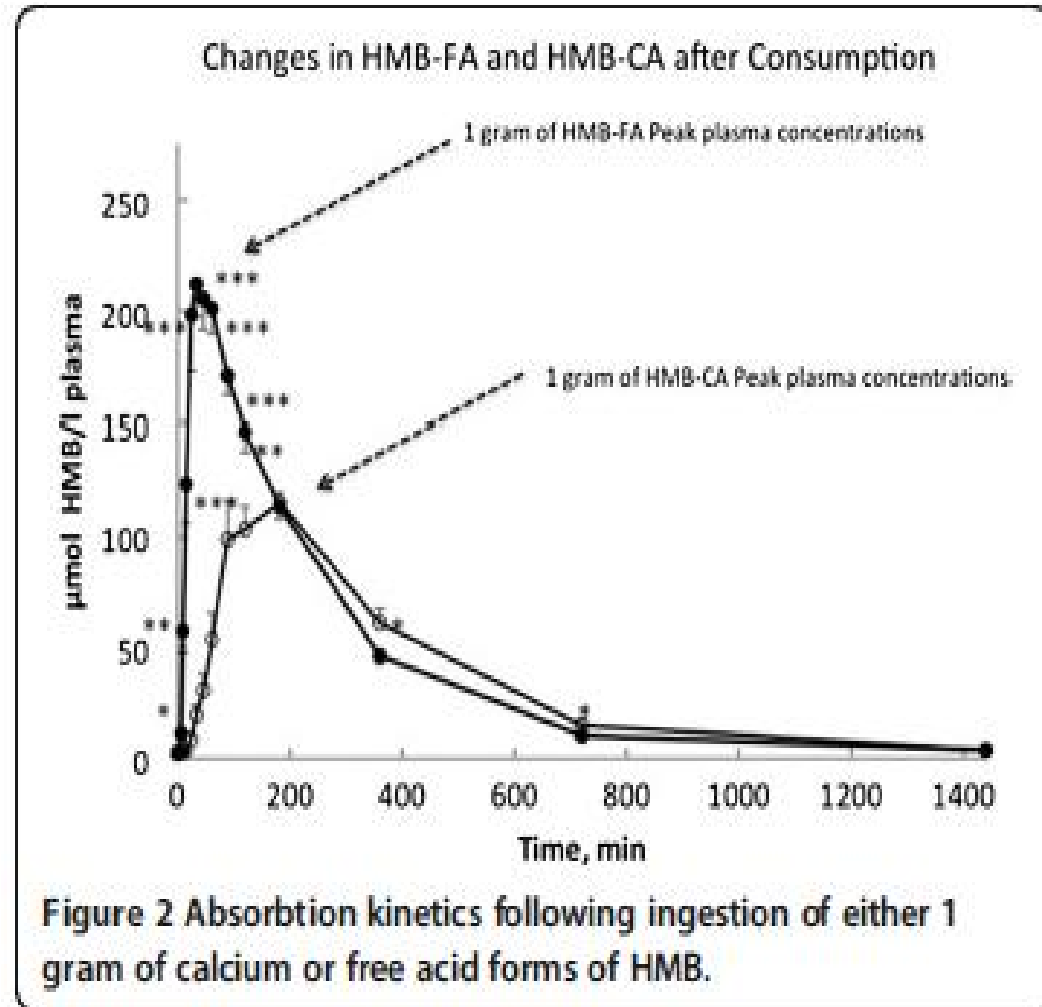
Origin of muscle loss	Study design	Effects	Reference
AIDS	HMB/Arg/Gln mixture (3/14/14 g per day) for 8 weeks	↑ lean body mass and improved immune status	Clark <i>et al.</i> ⁹⁷
Cancer	HMB/Arg/Gln mixture (3/14/14 g per day) for 24 weeks	↑ body weight and FFM	May <i>et al.</i> ⁹⁸
Cancer	HMB/Arg/Gln mixture (3/14/14 g per day) for 8 weeks	Trend towards an increased body mass	Berk <i>et al.</i> ⁹⁹
AIDS or cancer	HMB/Arg/Gln mixture (3/14/14 g per day) for 8 weeks	Decreased feeling of weakness, increased RBC, haematocrit, lymphocytes, eosinophils, and urea	Rathmacher <i>et al.</i> ¹⁰⁰
Chronic obstructive pulmonary disease	HMB (3 g/day) for 7 days	Improved pulmonary function, ↓CRP	Hsieh <i>et al.</i> ¹⁰¹
Chronic cardiac or pulmonary disease	Oral supplementation with proteins and HMB (1.5 g HMB/day) for 90 days	Decreased mortality, improved indices of nutritional status	Deutz <i>et al.</i> ¹⁰²
Chronic pulmonary disease	Oral supplementation with proteins and HMB (1.5 g HMB/day) for 12 weeks	Improved body composition, health-related quality of life, and muscle strength	Olveira <i>et al.</i> ¹⁰³
Critically ill trauma patients, bed rest, enteral nutrition	HMB (3 g/day), HMB/Arg/Gln mixture or placebo via feeding tube for 28 days	Improvement in nitrogen balance	Kuhls <i>et al.</i> ¹⁰⁴
Total knee arthroplasty	HMB/Gln/Arg mixture (2.4/14/14 g per day) for 4 weeks	Prevention of reduction of maximal strength of quadriceps muscle	Nishizaki <i>et al.</i> ¹⁰⁵
Hip fracture	HMB (3 g)/vitamin D/protein combination for 30 days	Accelerated healing, shortening immobilization period, ↑ muscle strength	Ekinici <i>et al.</i> ¹⁰⁶
Gastric bypass	HMB/Gln/Arg mixture (1.5/7/7 g per day) for 8 weeks	No benefits when compared with controls	Clements <i>et al.</i> ¹⁰⁷
Renal failure	HMB (3 g/day) for 6 months	No benefits	Fitschen <i>et al.</i> ¹⁰⁸
Rheumatoid arthritis	HMB/Gln/Arg mixture (3/14/14 g per day) for 12 weeks	No benefits when compared with placebo	Marcora <i>et al.</i> ¹⁰⁹

HMB- sarcopenická obezita

- ❖ Protein Vzestup LBM
(↑ proteosyntéza, ↓ proteolýza)
- ❖ Lipidy Pokles fat
mass- oxidace tuků Flux FFA, energie,
podpora MPS
- ❖ Cukry-působí proti inzulinorezistenci, GLUT 2 možná terapie diabetu, kardiovask onem Zlepšuje nutritivní flow (inzulin stimulace)
- ✓ *Stout* 48mužů sarcopen obezita- 12 týdnů HMB + tréning-
DXA:zlepšení

2 formy HMB

- Calcium- HMB (HMB-Ca)
- 1g peak za 120min
- 2. free-acid –HMB (HMB-FA)
- 0,8g peak za 30min



Nutrivigor



- **Kombinace HMB-Ca, vit D, bílkoviny**

- **Vitamín D:**

- metabolismus Ca, mineralizace kostí
- modulace růstu buněk
- ovlivnění neuromuskulárních fcí
- imunitních pochodů
- tlumení zánětu

- U seniorů ≥ 65 let pokles hladiny (25-OH vitD)- pokles svalové síly, (stisk ruky), pokles LBM (DXA)

- Hranice dostatečného zásobení **75nmol/l, tj 30ng/ml**

- 2 balení Ensure plus advance

- **3g CaHMB**

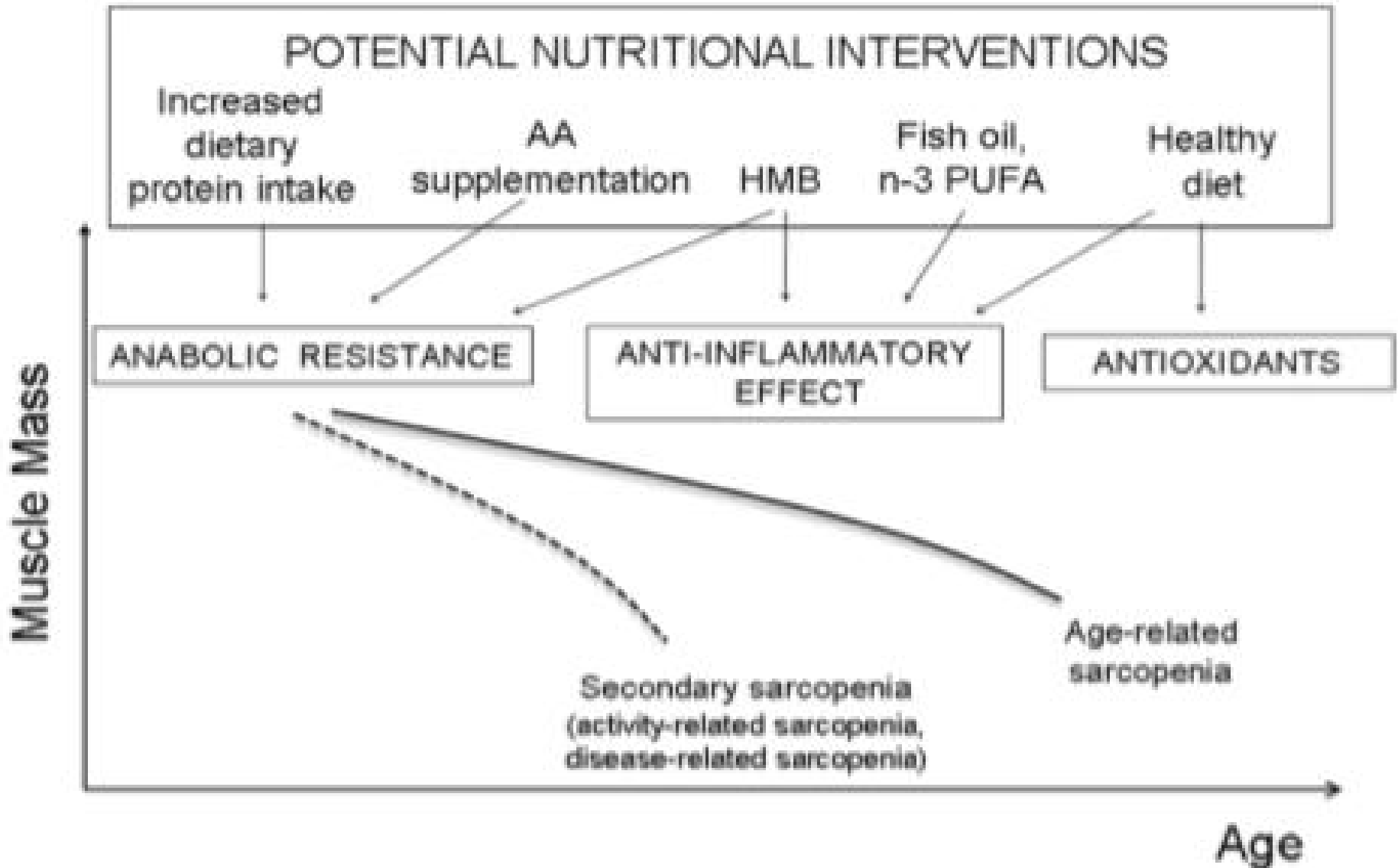
- **1000 IU vit D**

- **40g bílkovin**





Spojitost mezi nutriční a sarcopenií




Jak překonat anabolickou rezistenci

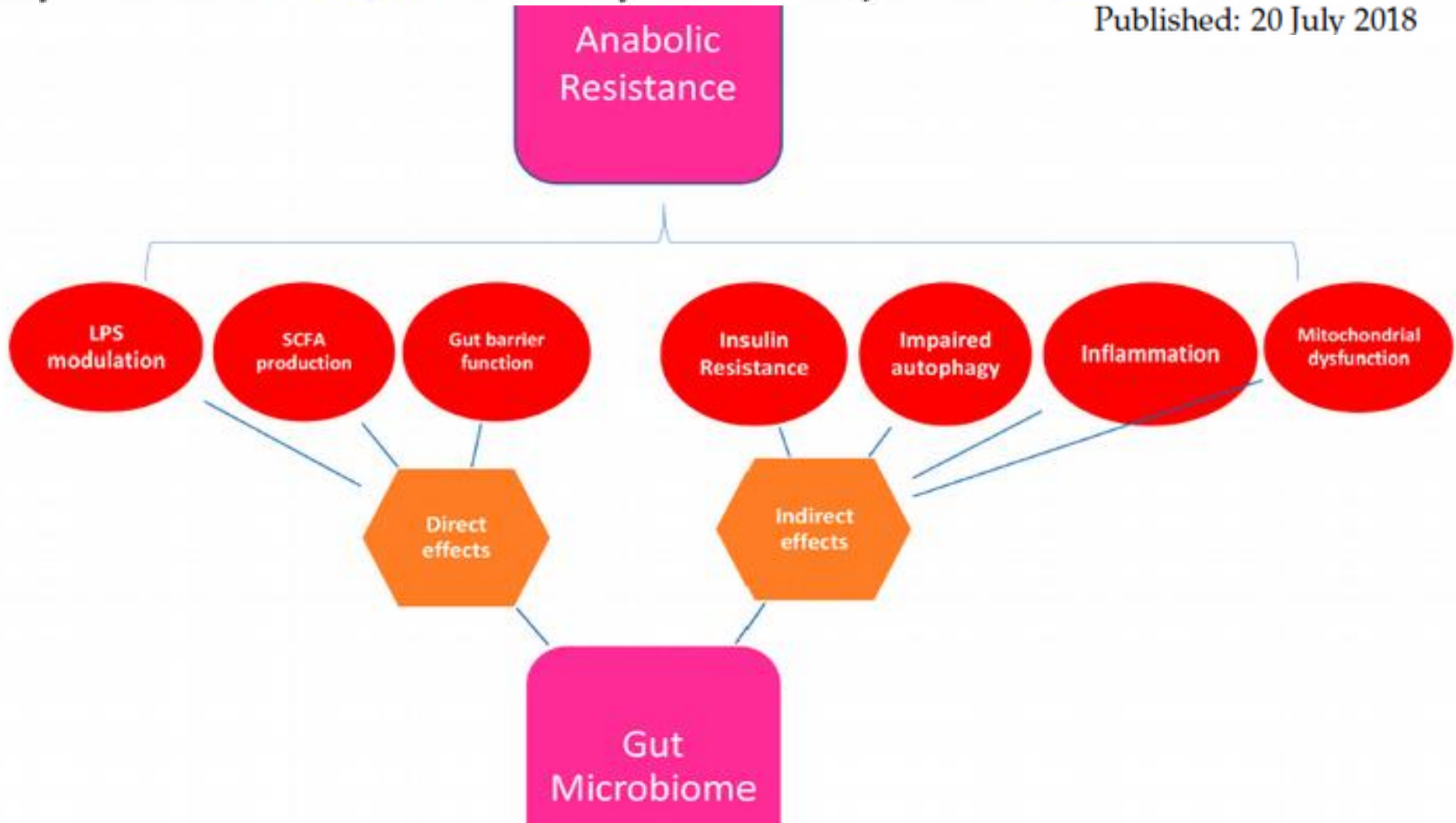
- **Jen extra AMK nestačí !!!**
- **Redukce MPB:** rekombinant GH, inzulín, beta-blokátory, anticytokiny
- Antioxidanty, ω 3MK
- **Stimulace MPS:** syrovátka, kasein
- *Nutritivní blood flow:* ACEI, AT 1 inhib, statiny, inzulin, **cvičení !!!**
- **Stimulace signálních kaskád MPS:** BCAA, leu, **HMB**
- **Střevní mikrobiom-** symbiotika (pre, probiotika), fekální Tx

Review

Dietary Protein and Muscle in Aging People: The Potential Role of the Gut Microbiome

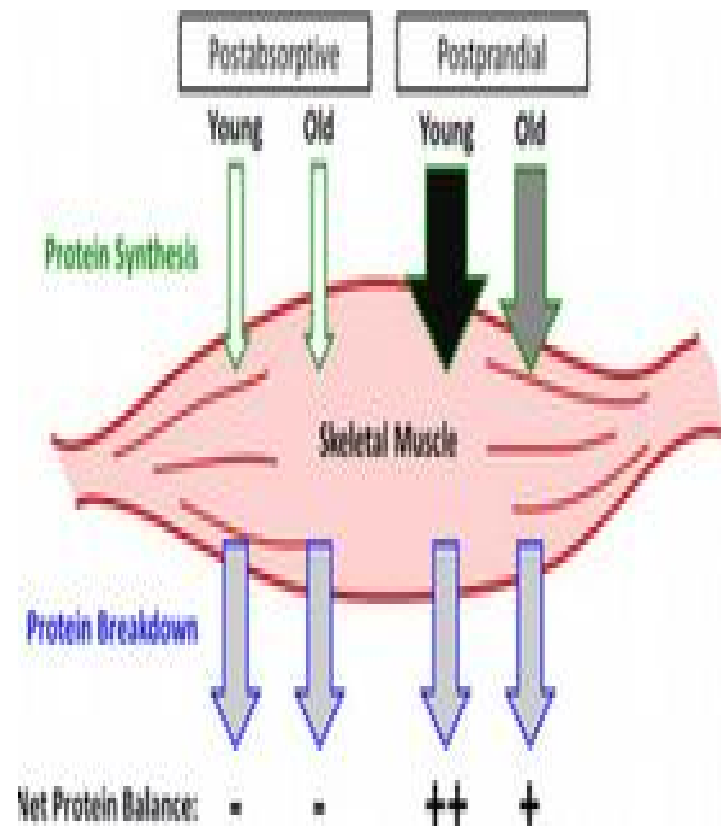
Mary Ni Lochlainn ^{1,2,*} , Ruth C. E. Bowyer ¹ and Claire J. Steves ^{1,2} 

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HMB má schopnost

- Omezit svalovou ztrátu nebo zvýšit její objem, stimulovat proteosyntézu postprandiálně. **ANABOLICKÝ EFEKT**
- zvýšit svalovou sílu (podmínkou je dostatečná hladina vit D > 30ng/ml 25 OH-vit D)
- zlepšit fyzickou výkonnost
- Zlepšit kvalitu svalové tkáně (LBM, FM), inzulinosenzitivitu
- Omezit negativní vliv zánětlivé reakce na metabolismus bílkovin ve svalech





HMB udrží svalovou hmotu u Masters atletů,
všeobecně u seniorské skupiny (ISSN)

Děkuji za pozornost