Cardiology Lett. 2012;21(3):201–203

Risk related to low cholesterol levels

Ginter E[1], Simko V[2]

[1]Slovak Medical University, Bratislava, Slovak Republic (emeritus), [2]State University New York, Downstate Medical Center at Brooklyn, USA

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Abstract. Presently accepted guidelines related to serum total cholesterol (CH) deal only with elevated levels. A desirable value is considered less than 5.2 mmol/L, marginal to elevated cardiovascular disease (CVD) risk is at 5.2 to 6.2 mmol/L; high risk is at CH above 6.2 mmol/L. This policy ignores findings where very low CH is associated with increased general mortality. Consequently, CH values lower than 4.2 mmol/L should represent an increased risk of general mortality. Fig. 3, Ref. 8, Online full text (Free PDF), www.cardiology.sk

Key words: cholesterol levels – cardiovascular mortality – total mortality – statins

Throughout the 19th until the mid 20th centuries there was an epidemic rise in CVD mortality in the United States (up to 800/100,000). Despite a continuing decline, in 2004 450,000 people still died of CVD in the US. More than 13 million North Americans are yearly diagnosed with coronary heart disease. The annual medical cost of CVD exceeds 150 billion USD.

Over the years it has been firmly documented that elevated CH (especially the low density lipoprotein LDL) is associated with risk of CVD. In response, preventive measures have been widely and indiscriminately introduced, including strict lowering of food cholesterol intake and a widespread use of lipid lowering medications . Expert consensus in 2001 (1) proposed guidelines for an ideal CH to be less than 5.2 mmol/L (less than 200 mg%), marginal risk for CVD at 5.2 – 6.2 mmol/L (200 – 239 mg%) and high CVD risk at CH over 6.2 mmol/L (over 240 mg%). In

From [1]Slovak Medical Univeristy, Bratislava, Slovak Republic and [2]State University New York, Downstate Medical Center at Brooklyn, USA,
Manuscript received February 29, 2012; accepted for publication March 1, 2012

Address for corespondence: RNDr. Emil Ginter, DrSc., Racianska 17, 831 02 Bratislava, Slovak Republic, e-mail: ginter.emil@mail.t-com.sk; Prof. V. Simko, MD, State University New York, Downstate Medical Center at Brooklyn, USA, e-mail: simko2@verizon.net

Riziko nízkych hladín cholesterolu

Ginter E[1], Simko V[2]

[1]Slovenská zdravotnícka univerzita, Bratislava, Slovenská republika (emeritus), [2]State University New York, Downstate Medical Center at Brooklyn, USA

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Abstrakt. V súčasnosti sa používa schéma na určenie rizika kardiovaskulárneho ochorenia, podľa ktorej je ideálna hladina celkového cholesterolu pod 5,2 mmol/L, medzná až riziková je oblasť 5,2 – 6,2 mmol/L a vysoko rizikové sú hladiny CH nad 6,2 mmol/L. Táto schéma nerešpektuje skutočnosť, že veľmi nízke hladiny cholesterolu zvyšujú celkovú mortalitu. Navrhujeme, aby sa za ideálne považovali hodnoty od 5,2 po 4,2 mmol/L a hodnoty pod 4,2 mmol/L by sa považovali vzhľadom na celkovú mortalitu za rizikové. Obr. 3, Lit. 8, Online full text (Free PDF), www.cardiology.sk

Kľúčové slová: hladiny cholesterolu – kardiovaskulárna mortalita – celková mortalita – statíny

Od začiatku 19. storočia až po rok 1950 narastal počet chorôb srdca v USA až po úroveň 800 úmrtí na 100 000. Potom začala kardiovaskulárna mortalita klesať. Napriek tomu v roku 2004 zapríčinili choroby srdca v USA 450 000 úmrtí, viac ako 13 miliónov ľudí trpelo na koronárne srdcové ochorenie a cena liečby prevyšovala 150 miliárd dolárov ročne. Zistenie, že jednou z hlavných príčin koronárneho ochorenia sú vysoké hladiny cholesterolu (CH), presnejšie nízkodenzitného lipoproteínu (LDL), viedlo k prudkému, až k histerickému odmietaniu cholesterolu v potrave a k boju proti vysokým hladinám CH v krvi. V roku 2001 klasifikoval panel odborníkov (1) schému, podľa ktorej je ideálna hladina cholesterolu pod 5,2 mmol/L (pod 200 mg%), medzná až riziková je oblasť 5,2 – 6,2 mmol/L (200 – 239 mg%) a vysoko rizikové sú hladiny CH nad 6,2 mmol/L (nad 240 mg%). Túto schému prevzala aj väčšina európskych inštitúcií.

Zo [1]Slovenskej zdravotníckej univerzity v Bratislave, Slovenská republika a [2]State University New York, Downstate Medical Center at Brooklyn, USA
Do redakcie prišlo dňa 29. februára 2012; prijaté dňa 1. marca 2012

Adresa pre korešpondenciu: RNDr. Emil Ginter, DrSc., Račianska 17, 831 02 Bratislava, Slovenská republika, e-mail: ginter.emil@mail.t-com.sk; Prof. V. Simko, MD, State University New York, Downstate Medical Center at Brooklyn, USA, e-mail: simko2@verizon.net

Figure 1 Mortality from all causes and cholesterol level. According to Multiple Risk Factor Intervention trial (2).
Obrázok 1 *Závislosť úmrtnosti zo všetkých príčin od hladiny cholesterolu. Podľa Multiple Risk Factor Intervention trial (2).*

retrospect, it is surprising that these guidelines did not consider the previously-reported higher general mortality (that includes CVD mortality) at a CH level below normal.

The Multiple Risk Factor Intervention trial (MRFIT) in the 1980s recruited more than 350,000 men aged 35 – 57 who were followed for CVD risk and CH (2). This project confirmed correlation of CVD risk with the increase in CH. However, there was a surprising finding of increased general mortality in cohorts with abnormally low CH **(Figure 1)**. Mortality was higher when CH was below 4.2 mmol/L. In CH lower than 3.6 mmol/L general mortality exceeded the mortality when CH was elevated to 7 mmol/L and higher. This and additional studies indicate the need to warn the medical community to pay attention not only to elevated CH but also to be aware of health risk at abnormally low CH.

Another report (3) followed mortality in patients aged over 65 in relation to CH. Mortality was inversely related to CH. As in the other study (2), the general mortality at lower CH was excessive when CH was below 4.2 mmol/L **(Figure 2)**. A Finnish study (4) documented higher general mortality in subjects with CH less than 5 mmol/L when these were compared with individuals having CH more than 6 mmol/L. Similar findings were reported in an aged Honolulu population (5). In another study, diabetics type 2 who had LDL-C below 2.8 mmol/L had a higher risk of malignancy (6). The association persisted when patients who were followed for less than 2.5 years were excluded. Such proof runs contrary to previous criticism that the association between low CH and cancer is the result of inclusion of patients with missed cancer diagnosis.

Remarkable also are the results on general mortality in relation to serum CH in patients presribed statins. Indivi-

Prekvapuje, že tvorcovia týchto noriem nebrali do úvahy štúdie, ktoré túto normu popierajú najmä vzhľadom na úmrtnosť pre všetky príčiny, čo je významnejší ukazateľ ako kardiovaskulárna mortalita.

The Multiple Risk Factor Intervention trial (MRFIT) realizovaný v 80-tych rokoch sledoval vyše 350 000 mužov vo veku 35 – 57 počas 10 rokov na kardiovaskulárne rizikové faktory, vrátane hladiny celkového CH v krvi (2). Štúdia dokázala, že kardiovaskulárne príhody skutočne stúpajú so zvyšovaním hladiny CH, ale súčasne zistila prekvapivý nárast v celkovej úmrtnosti pri nízkych hladinách CH **(obrázok 1)**. Vzhľadom na celkovú úmrtnosť boli optimálne hladiny CH v rozsahu 4,2 – 5,6 mmol/L, ale pod 4,2 mmol/L začala úmrtnosť stúpať a pri hladine pod 3,6 mmol/L bola podstatne vyššia ako pri rizikových hladinách CH okolo 7 mmol/L. To znamená, že odporúčanie ideálnych hladín CH pod 5,2 mmol/L je chybné, pretože nestanovuje hranicu pre veľmi nízke hladiny CH, pri ktorých začína celková úmrtnosť stúpať. Cieľom tejto štúdie je stanoviť hranicu nebezpečne nízkych hladín CH.

U takmer 7 000 hospitalizovaných pacientov vo veku nad 65 rokov sa sledovala závislosť ich úmrtia od hladiny CH počas 20 rokov (3). Ukázalo sa, že ich mortalita bola inverzne závislá od hladiny CH. Podobne ako v predchádzajúcej štúdii bola celková úmrtnosť mimoriadne vysoká pri hladine pod 4,2 mmol/L **(obrázok 2)**.

Šesťročné sledovanie ľudí nad 70 rokov vo Fínsku ukázalo, že osoby s hladinou CH pod 5 mmol/L mali vyššie riziko úmrtia ako osoby s hladinou CH nad 6 mmol/L (4). Podobné výsledky sa získali u starších osôb v Honolulu (5). U diabetikov 2. typu hladiny LDL cholesterolu pod 2,80 mmol/L boli spojené so zvýšeným rizikom rakoviny (6). Tento vzťah pretrvával aj po vylúčení pacientov sledovaných menej ako 2,5 roka. To vylučuje obvyklé staršie námietky, že vzťah nízky CH a kancerogenéza vyplýva so zaradením pacientov s nediagnostikovanou rakovinou.

Pozoruhodné výsledky sa získali pri sledovaní vplyvu statínov na celkovú úmrtnosť pri rôznych hladinách CH. Pri sledovaní úmrtnosti pacientov liečených šesť rokov simvastatínom (7) sa ukázalo, že celková úmrtnosť pri hladinách CH pod 4,1 mmol/L bola vyššia ako pri hladinách CH nad 7,2 mmol/L **(obrázok 3)**.

Pri nízkych hladinách CH je nepriaznivo ovplyvnený celý imunitný systém. Nízke hladiny CH narušujú jeho efektivitu, pretože CH je potrebný pre normálnu funkciu makrofágov a lymfocytov (8). Pri porovnaní skupiny mužov s priemernými hladinami celkového CH 3,9 mmol/L so skupinou s hladinami 6,8 mmol/L sa ukázalo, že skupina s nízkym CH mala menej cirkulujúcich lymfocytov a menej T-buniek. T-bunky likvidujú nádorové bunky a pri ich nízkych hladinách je riziko kancerogenézy zvýšené.

Cholesterol znižujúce statíny sú v súčasnosti najviac predpisované lieky na celom svete. V roku 2011 asi 21 miliónov pacientov v USA užívalo statíny. Je zrejmé, že voľba kandidátov na terapiu statínmi musí byť premyslená.

duals using simvastatin for six years (7) had higher general mortality at CH less than 4.1 mmol/L than those with CH over 7.2 mmol/L **(Figure 3)**.

We can only speculate on the clinical significance of these findings. The metabolism of CH is a variable not solely related to atherogenesis. General mortality has wider all- inclusive health implications in addition to CVD. In the general mortality the CVD mortality is only an epiphenomenon to complications of atherosclerosis. Population studies reporting higher mortality at low CH did not include potential confounding variables contributing to general mortality, body mass index, smoking, chronic infection, overall immune integrity and other specific, non CVD related, health disorders.

This review warns of oversimplification. CH is a natural metabolite essential for biological integrity. Together with other lipids it preserves normal cellular function, especially of macrophages and lymphocytes (8). An abnormally low body pool of CH may compromise the immune system (or vice versa). Males with CH 3.9 mmol/L had fewer circulating lymphocytes than subjects with CH 6.8 mmol/L. It is possible that with decreased function of T-lymphocytes there may be impaired resistance to cancerogenesis.

This warning call is not to be considered a battlecry against management of disorders related to abnormally high CH. Past evidence and the benefit of management of hyperlipoproteinemia have been established beyond doubt. A wise clinician always weighs the benefit of rational therapy against the risk of overtreatment. Cholesterol is not a foreign substance that has to be scrupulously eliminated. When prescribing lipid-lowering medications the physician has to carefully adjust the intensity of therapy to the extent of abnormality of the lipid profile.

Cholesterol-lowering statins are among the most widely presribed drugs in the world. In 2011 nearly 21 million patients in the United States were prescribed statins. Whether the extent of statin administration is too high or still inadequate has been contested for years. Nevertheless it is becoming obvious that the selection of candidates for CH lowering therapy has to be performed judiciously.

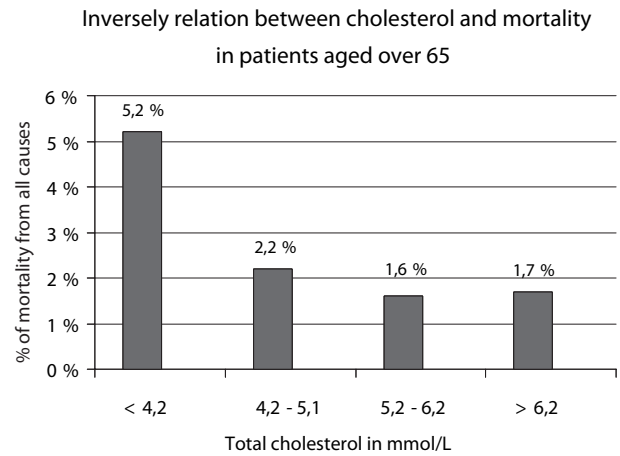

Figure 2 Total mortality of old people followed over 20 years. According to 3.
Obrázok 2 *Celková úmrtnosť starých ľudí sledovaných vyše 20 rokov (3)*

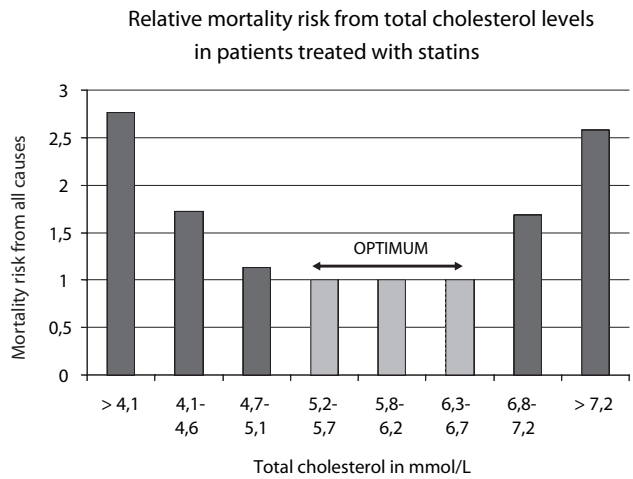

Figure 3 Relative mortality risk from all causes and cholesterol levels in patients treated with simvastatin. According to 7.
Obrázok 3 *Závislosť relatívneho rizika úmrtia zo všetkých príčin od hladiny cholesterolu u pacientov liečených simvastatínom (7).*

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