C REACTIVE PROTEIN AND CARDIOVASCULAR RISK IN CASES WITH DIABETES MALLITUS TYPE II

Munevera Bećarević[1],[a]
Duška Bećirović[b],
Azijada Beganlić[c],
Olivera Batić-Mujanović[c],
Suad Sivić[d]

Public Health institution in Banovici[a]
Public Health institution in Zivinice[b]
Department for family medicine – Public Health Centre Tuzla)[c]
Organization and health economy, Department of public health in Zenica, University of Zenica, Faculty of health[d]

Original scientific paper

ABSTRACT

Introduction: Factors of cardiovascular risk (CVR) are often grouped in cases with diabetes mellitus (DM) with significant increasment of risk for CV disease . The aim of this research is to determine the frequency of CVR and and total CVR in cases with DM and to investigate connection of CRP of other factors of CVR in total cardiovascular risks. Material and methods: In 92 cases with DM weist values were taken as well as body mass index (BMI), blood pressure, sugar in blood, cholesterol, triglycerides, C reactive protein (CRP) and according to SCORE system the 10 year period of CVR were determined. Results: Out of 92 tested cases with age 55,22± 8,3 years, 63,05% were males and 36,95% were women, 81,5% were with values of sugar in blood >7mmol/l, 44,6% were with values of HbA1C>7% and 63,0% >6,5%. The value of cholesterol were >4,5mmol/l in 87%, triglycerides >1,7mmol/l in 78.3% of tested cases. 81,5% of tested cases were overweight and 49% with larger weight values. Average cardiovascular factor according to SCORE system was 3, 92± 3,7% with significant difference among sexes (M-4,86; W-2,32, p<o,05). According to height value CRP (>3mg/l) 52% of tested cases were with high cardiovascular risk. There is significant positive correlation between CRP and cholesterol level (p<0, 01), triglycerides, blood in sugar, HbA1c and upper values of blood pressure (p<0, 05). Significant correlation between CRP and total cardiovascular risk (p=0, 63) was not evident. Conclusion: Cases with diabetes mellitus have high level of non regulated cardiovascular risk factors. Even though there is significant correlation between CRP and and pressure values, sugar in blood, HbA1c, cholesterol, triglycerides, significant correlation between CRP and total cardiovascular risk in cases with diabetes mellitus is not evident.
Key words: *C reactive protein, cardiovascular risk, diabetes melitus*

INTRODUCTION

Nearly half of all events related to cardiovascular disseases are evident in helath individuals with some or none of traditional risk factors including dislipidemy (Ridker et al., 2003). This is the main reason why the focus is evident on other factors such as inflamatory markers in development of aterosclerosis and cardiovascular dissese (Farmer and Torre-Amione, 2002; Pearson et al., 2004).

[1]**Correspondence to:**
Bećarević Munevera, Public Healt institution in Banovici, Bosnia and Herzegovina
Banovici, Bosnia and Herzegovina
Phone: 0038761 282 873
E-mail: b.munevera@gmail.com

This resulted in search for biomarkers which will improve detection of cardiovascular risk among so called healthy individulas (Ridker et al., 2003). Among all possible candidates, clinicaly usefull biomarker for cardiovascular risks is C-reactive protein (CRP) partialy to high sensibility (Ridker, 2003). Several prospective studies showed that highly sensible (hs) CRP is independent predictor of future risk for cardiovascular events among helathy individuals such as cases with acute coronary syndrome (Clearfield, 2005).

Some researches have showed that hs-CRP is strong and independent predictor of future caediovascular events incuding heart attack, ishemic stroke, peripheral vascular disseases and sudden death amnog individuals without known cardiovascular dissease (Ridker, 2001; Ridker, 2003). In group of 1086 healthy middleaged men, tested cases with CRP value in highest quartal were exposed to stroke or periferal vascular dissease risk twice higher (p= 0,02) and three times higher heart attack risk (p<0,001) in comparing to tested cases with CRP in the lowest quartal, independantly to other cardiovascular risk factors (smoking, dislipidemy) (Ridker et al., 2005). The level of hs-CRP is related to coronary events that happened even 15 years later and corellation between hs-CRP and heart attack risk is proven on tested cases without other risk factors (Sakkinen et al., 2002). After research of relation of inflamatory markers and stroke, American Heart Association (AHA) and centres for contorle and illness prevention (CDC) have recomended determination of highly sensible (hs) CRP as more sensitive test for prediction of vascuklar dissesase in comparing to traditional methods of CRP determination (Pearson, 2003; Ridker, 2003).positive correlation between hs-CRP and lasting of diabetes strongly suggests that information on imflamatory condition, even in young cases with diabetes with case of illnes in short time period, can provide clinical importance becouse aterosclerosis and vascular damadges begin in childhood (Jarvisalo et al., 2002).

Data on sex and age of tested case as well as the lenght of dissease, family anamnese and personal i.e. comornidity were takem. Documentation provided data on concentration of sugar in blood, cholesterol, triglicerids and C reastive protein. Patients were taken values in blood preasure, weist values, weight and height and bodz mass index (BMI) was calculated.

According to SCORE scalar system all patients were dtermined for 10 year cardiovascular risk (CVR). According to SCORE scalar system CVR is divided in low CVR (SCORE- 0), medium CVR (SCORE 1-5), High CVR (SCORE 5-10) and very high CVR (SCORE > 10).

Based on values of CPR, cardiovascular risk in tested cases was detrmined. Recomendations of AHA were used as criteria and according to them, based on CRP concentration, cardiovascular risk is divided on low (CRP < 1mg/l), medium (CRP 1 – 3 mg/l), and high (CRP > 3 mg/l). Statistical processing ofa data was perfomed in SPSS 16 programme. During analysis descriptive statistical methods were used (frequency, arithmetica values, standard mistake and standard deviation) and Pearsons' correlation. Arithmetic value of taken parameters was determined as well as degree of control of tested risk factors.

According to Pearsons' correlation the type of CRP concentration was calculated alond with tested risk factors as well as total cardiovascular risk according to SCORE system. For statistical signiffance of ''p'' value ussual level of signiffance $p < 0,05$ was taken.

RESULTS

Average study was conducted and it covered 92 tested cases, 58 (63,05%) males (M) and 34 (36,95%) females (F), with average age 55,22 (±8,3, n=92) years of life. Tested subjects were treated of diabetes melitus in average of 5,07 (±3,75) years.

Out of 92 tested subjects, 81,5% were with sugar in blood values of je imalo >7mmol/l, 44,6% of tested subjects have had HbA1c >7%, a 63,0% > 6,5%. Cholesterol values > 4,5 mmol/l je were evident in 87%, a triglicerds values a > 1,7mmol/l 78,3% of tested subjects. 81,5% of tested subjects were overweight, a 49% were with larger weist values, blood preasure values >140/90 were evident in 39,1% of tested subjects (Figure 1).
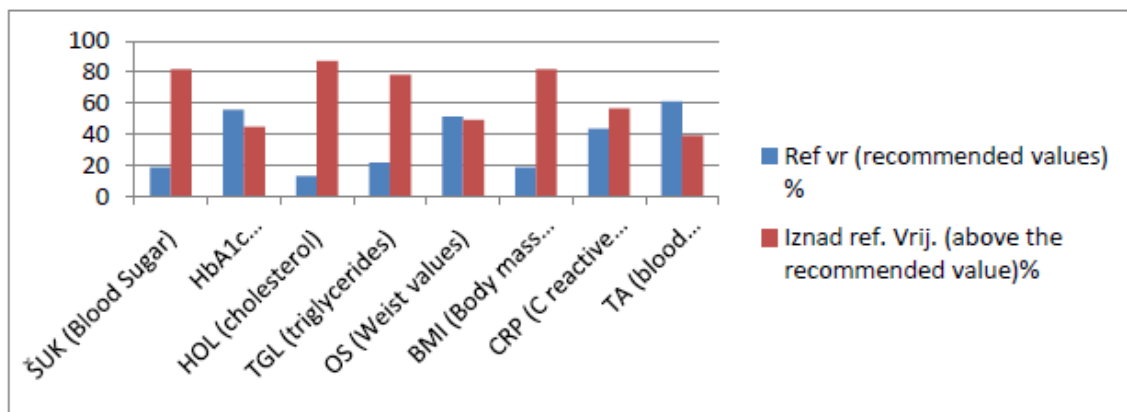
Figure 1. Degree of cardiovascular risk-factors regulation

Legend: ŠUK- sugar in blood; HbA1c- hemoglobinised hemoglobine; Hol- cholesterol; TGL- triglic-erids; OS- weist values; BMI- body mass index; CRP- C-reaktive proteins; TA- blood preasure; ref. Vr.- recomended values.

According to values of CRP, 56,5% of tested subjects have had high values of CVR (CRP >3 mg/l), 25% medium and 18,5% low CVR (Figure 2, Table 1).
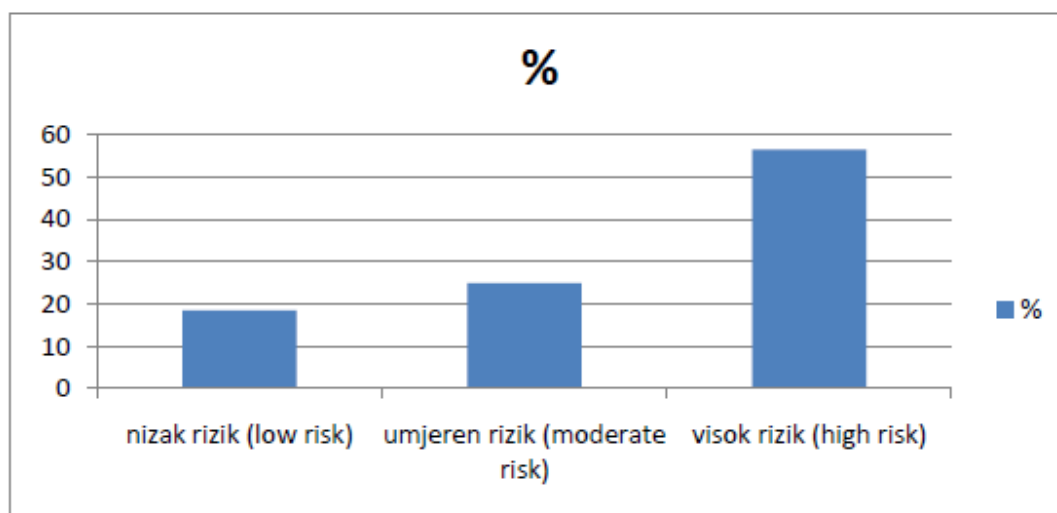

Figure 2. Cardiovascular risk according to the concentration of CRP

Average CVR according to SCORE scalar system is 3,92% (SD= 3,7) with signiffcant difference among sexes (M- 4.86; F- 2,32, p<0,05). According to SCORE scalar system the most of tested subjects, 59 of them (64,13%), were having medium and 4 of them (4,34%) were with low KVR (Table 1).

Table 1. Cardiovascular risk by SCORE system and the level of CRP

KV rizik (CV risk)	Frequency SCORE	Percent SCORE	Frequency CRP	Percent CRP
Nizak rizik (low risk)	4	4,34	17	18,5
Umjeren rizik (moderate risk)	59	64,13	23	25,0
Visok rizik (high risk)	24	26,08	52	56,5
Vrlo visok rizik (very high risk)	5	5,43		
Ukupno (total)	92	100	92	100

Legend: CV-cardiovascular risk; CRP-C reactive protein

There is difference in levels of cardiovascular risks in tested subjects depending on used criteria. According to SCORE scalar system the most of tested subjects are with medium and according to CRP the most of tested subjects are with high CVR (Figure 3).
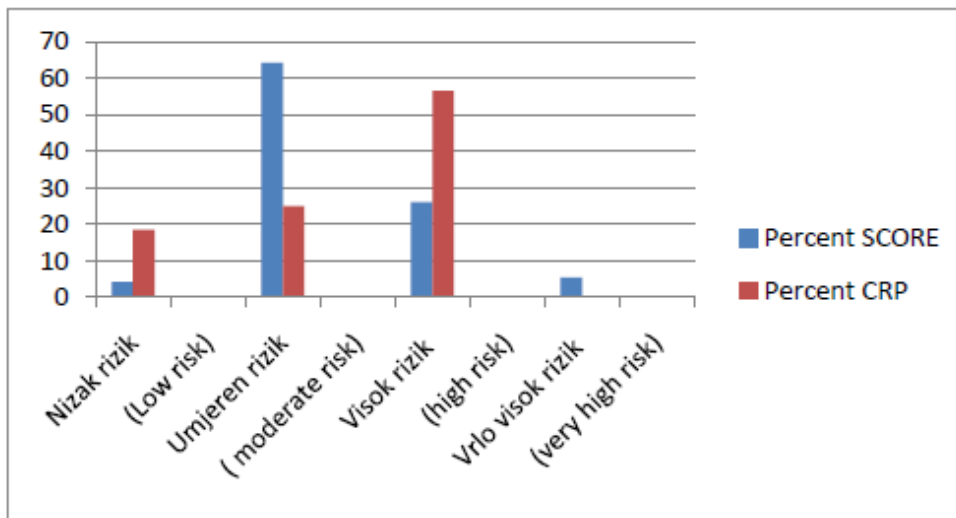

Figure 3 Cardiovascular risk according to the level of CRP and the SCORE pointing system

Legend: CRP- C reactive protein

There is signifficant positive correlation between CRP and cholesterol level (p<0,01) , triglicerids, Sugar in blood, HbA1c and level of blood preasure (p<0,05). Signifficant correlation of CRP and total CVR isn't proven (p=0,63) (Table 2).

Table 2. Correlation of CRP and other risk factors

Risk faktors	Pearson Correlation	Statistical significance	Number
Blood Sugar	0,149	0,156	92
HbA1c	0,235*	0,043	75
cholesterol	0,258	0,013	92
triglycerides	0,314	0,002	92
Weist values	0,262	0,012	92
Body mass index	O,150	0,160	92
C- reactive protein	0,080	0,450	92
blood pressure	0,219	0,036	92
smoking status	0,130	0,217	92
cardiovascular risk	0,50	0,635	92

DISCUSSION

High level of hs-CRP is declared as independent predictor of cardiovascular risk related to metabolic syndrome (Ridker et al., 2003). Increased hs-CRP is related to abdominal overweight in men with aterogenic dislipidemy, important clinical marking of metabolic syndrome (Lemieux et al., 2001). In our research, positive correlation between values of weist and level of CRP in blood is not proven.

A study conducted among pilots in Serbia and Monte Negro have shown that BMI in values from 25 do 30 kg/m² was evident 64%, and over 30 kg/m² in 7,5% of tested subjects (Jovelić et al., 2005). The same research hev shown that all characteristics of MS except from blood preasure were statisticlly signifficantlly with concentration of CRP in plasma, and level of CRP have grown with increasment of number of MS characteristics (Jovelić et al., 2005).

Some studies have shown that the level of highly sensitive CRP positively correlates with level of triglicerids and level of triglicerids for HDL, but not with other lipids (Schram ET AL., 2003; Ladeia ET ALL., 2006). There is positive correlation between level of CRP and level of cholesterol (p=0,002) and triglicerids (p=0,012) in blood in our research.

Some researches haven't proven correlation between hs-CRP and glikemy (Coulon et al., 2005). Also, the fall of hs-CRP level after intensive glikemy control in diabetes melitus type I is not proven (Coulon et al., 2005). However, positive correlation between level of CRP and concentration of sugar in blood 120 minutes after meal is confirmed as positive (p=0,043) and values HbA1c (p=0,013)on our tested subjects. Researches have also shown that level of hs-CRP is signifficantly larger in older tested subjects, overweight subjects, subjets with diabetes melitus, metabolica syndrome, increased values of weist, hypertrigliceridemia, higher level of LDL, positive CVB and lower body activity without these risk factors (P <0,05) (Schaumberg et al., 2005). Our research have proven egzistence of signifficant positive correlation between CRP and choletserol level (p<0,01) , triglicerids, sugar in blood, HbA1c and level of blood preasure (p<0,05). Research have shown that the level of hs-CRP is signifficantly larger in older test subjects, overweight subjects, subjects with diabetes melitus, metabolic syndrome, increased weist values, hypertrigliceridemia, higher level of LDL, positive CVB and lower body activity without these risk factors (P <0,05) (Baghshani et al., 2013). Our research have proven the egzistence of signifficant positive

correlation between CRP and level of cholesterol (p<0,01) , triglicerids, sugar in blood, HbA1c and level of blood preasure (p<0,05). Testing of healthy pilots have shown that CRP is not independent predictor of preclinical atherosclerosis and can be used for some other factors action, esspecially of visceral overweightness on preocess of aterogenesis (Jovelić et al., 2009). According to CRP level almos 52% of our tested subjects deal with high cardiovascular risk, while according to SCORE scalar system the largest number of teste subjects (64,13%) have medium cardiovascular risk. Several epidemiological researches point to dissapointing disadvantages in research and proper treatment of hypertension and dislipidemy in German with minimal improvement during past decades (Stark et al., 2011; Rückert et al., 2012; Raum et al., 2008).

According to some results only 7% in men and 13% in women with hypertension have controled blod preasure value (<140/90 mmHg) (Gasse et al., 2001). According to some results 64% of tested subjects with and 49% tested subjects without diabetes melitus type II in life age from 45 to 74, have been sufficiant or insufficiant medical treatment of increased blood preasure (Rückert et al., 2012). Tested subjects diabetes who were withh the highest coeficient of uncontroled comorbidity without pharmacotherapy were younger men with lower BMI and without history of cardiovascular disseases, and those with additional risk factors (diabetes, overweightness) were more aware of risk and treated more often but with lesser possibility of risk factors control gaining (Rückert et al., 2012). Overweight cases deal with hypertension more often and are treated in more complicated way but are more aware of it. Looks for well controled blood preasure in treated hypertensive tested subjects are signifficantly smaller in overweight test subjects (Bramlage et al., 2004).

Among hypertensive tested subjects without diabetes melitus (n = 5012), there were 29,2%, those with BMI values <25 were dealing with controled hypertnsion (41,2% were with uncontroled and 29,6% were in process of medical treatment) in comparing to those 28,6% with BMI values ≥ 30 (50,9% uncontroled and 20,5% in process of treatment) (Rückert et al., 2012). Research conducted in Sweden have proven direct reversible relation of high weist values with uncontroled hypertension in hypertensive 60 year old tested subjects with and without diabetes melitus (Carlsson et al., 2009).

14

Therefore, patients with additional risk factors (over-weightnes and diabetes) can be more aware of their blood preasure and treated more often, but in over-weight cases blood preasure ≥ 140/90 mmHg is more evident regarding medical treatment process. Our research have shown high degree of blood preasure control. Nearly 60,9% of tested subjects have recomended blood preasure value. However, 18,5 % of our tested subjects were dealing with recomended values ob BMI and 51% were having recomended weist values. Males with diabetes melitu type II without hypertension and previous MI were having more chance for nonregulated dislipidemy (Rückert et al., 2012).

Our tested cases were having high degree of nonregulated dislipidemy, 87% were havin cholesterol level and 78,3% level of triglicerids above recomended values.

CONCLUSION

Patients with diabetes melitus have high level of non-regulated CVR factors. Even though there is significant correlation between CRP and blood oreasure values, sugar in blood values, HbA1c, cholesterol, triglicerids, significant correlation between CRP and total CRV isn't proven according to SCOR scalar system in cases with diabetes melitus.

REFERENCES

Baghshani, MR., Rahsepa, AA. Ardabili, HM., Andalibi, MSS., Parizadeh, SMR et al. (2013) Association between C-reactive protein, pro-oxidant-antioxidant balance and traditional cardiovascular risk factors in an Iranian population. *Ann Clin Biochem*. 50:115-121.

Bramlage. P., Pittrow, D., Wittchen, HU., Kirch, W., Boehler, S., Lehnert, H., Hoefler, M., Unger, T. & Sharma, AM. (2004). Hypertension in overweight and obese primary care patients is highly prevalent and poorly controlled. *Am J Hypertens*. 17:904–910.

Carlsson, AC., Wandell, PE., Journath, G, de Faire U and Hellenius, ML (2009). Factors associated with uncontrolled hypertension and cardiovascular risk in hypertensive 60-year-old men and women–a population-based study. *Hypertens Res*, 32:780–785.

Clearfield, MB. (2005). C-reactive protein: a new risk assessment tool for cardiovascular disease. *J Am Osteopath Assoc*,105(9):409-416.

Coulon, J., Willems, D., and Dorchy. H (2005). Increase in C-reactive protein plasma levels during diabetes in infants and young adults. *Presse Med*,34:89–93.

Farmer, JA. and Torre-Amione, G. (2002). Atherosclerosis and inflammation [review]. *Curr Atheroscler Rep*.4:92-98.

Gasse, C., Hense, HW., Stieber. J., Doring, A., Liese, AD., and Keil. U. (2001). Assessing hypertension management in the community: trends of prevalence, detection, treatment, and control of hypertension in the MONICA Project, Augsburg 1984–1995. J Hum Hypertens 15:27–36.

Jarvisalo, MJ., Harmoinen, A., Hakanen, M., Paakkunainen, U., Viikari, J., Hartiala, J., Lehtimaki, T., Simell, O., and Raitakari, O. (2002). Elevated serum C-reactive protein levels and early changes in healthy children. *Arterioscler Thromb Vasc Biol*, 22:1323–1328.

Jovelić, A., Rađen, G., Jovelić, S., and Marković, M. (2005). Povezanost C-reaktivnog proteina i karakteristika metaboličkog

sindroma kod pilota Vojske Srbije i Crne Gore. *Vojnosanitetski Pregled*, 62(11): 811−819.

Jovelić, A., Rađen, S., Hajduković, Z., and Čanji, T. (2009). Povezanost nivoa C-reaktivnog proteina i prekliničke karotidne arteriuskleroze kod vojnih pilota. *Vojnosanitetski Pregled,* 66(6): 465–471.

Ladeia, A.M., Stefanelli, E., Ladeia-Frota, C., Moreira, A., Hiltner, A., and Adan, L. (2006). Association Between Elevated Serum C-Reactive Protein and Triglyceride Levels in Young Subjects With Type 1 Diabetes. *Diabetes Care*, 29(2): 424-426.

Lemieux, I., Pascot, A., Prud'homme, D., Alméras, N., Bogaty, P., Nadeau, A., et al. (2001). Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol*, 21:961-967.

Pearson, TA., et al. (2003). *Circulation, 107*: 499-511. Available at: http://circ.ahajournals.org/cgi/content/full/107/3/499

Pearson, TA., Mensah, GA., Hong, Y., Smith, SC Jr, for the Centers for Disease Control and Prevention and the American Heart Association Workshop on Markers of Inflammation and Cardiovascular Disease. CDC/AHA workshop on markers of inflammation and cardiovascular disease: application to clinical and public health practice: overview. *Circulation* 2004; 110:543-544.

Raum, E., Lietzau, S., Stegmaier, C., Brenner, H., and Rothenbacher, D. (2008). For the majority of patients with diabetes blood pressure and lipid management is not in line with recommendations. Results from a large population-based cohort in Germany. *Pharmacoepidemiol Drug Saf*, 17:485–494.

Ridker, PM. (2001). High-sensitivity C-reactive protein: Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease.*Circulation,103*:1813-1818.

Ridker, PM. (2003). Circulation, 107:363-369. Available at: http://circ.ahajournals.org/cgi/content/full/107/3/363

Ridker, PM. (2003). Clinical application of C-reactive protein for cardiovascular disease detection and prevention [review]. *Circulation,107*:363-369.

Ridker, PM., Buring, JE., Cook, NR., and Rifai, N. (2003). C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. *Circulation,107*:391-397.

Ridker, PM. (2003). Cardiology Patient Page. C-reactive protein: a simple test to help predict risk of heart attack and stroke. *Circulation,108*:e81-e85.

Ridker, PM. for the JUPITER Study Group. (2003). Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: Rationale and design of the JUPITER trial [review].*Circulatio,108*:2292-2297.

Ridker, PM., Rifai, N., Bradwin, G., and Buring, JE. (2005). Non-HDL cholesterol, apolipoproteins A-l and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. *JAMA*, 294:326-333.

Rückert, IM., Schunk, M., Holle, R., Schipf, S., Völzke, H., Kluttig, A., Greiser, KH., Berger, K., Müller, G., Ellert, U., et al. (2012). Blood pressure and lipid management fall far short in persons with type 2 diabetes: Results from the DIAB-CORE Consortium including six German population-based studies. *Cardiovasc Diabetol*, 11:50.

Sakkinen, P., Abbott, RD., Curb, JD., Rodriguez, BL., Yano, K., and Tracy, RP. (2002). C-reactive protein and myocardial infarction. *J Clin Epidemiol,*55:445-451.

Schaumberg, DA., Glynn, RJ., Jenkins, AJ., Lyons, TJ., Rifai, N., Manson, JE., Ridker, PM., and Nathan, DM. (2005). Effect of intensive glycemic control on levels of markers of inflammation in type 1 diabetes mellitus in the Diabetes Control and Complications Trial. *Circulation*, 111:2446–2453.

Schram,bMT. Chaturvedi, , Schalkwijk, C., Ebeling, P., Fuller, JH., and Stehouwer CD. (2003). Vascular risk factors and markers of endothelial function as determinants of inflammatory markers in type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetes Care, 26:2165–2173.

Stark, RG., Schunk, MV., Meisinger, C., Rathmann, W., Leidl, R. and Holle, R (2011). Medical care of type 2 diabetes in German disease management programmes: a population-based evaluation. Diabetes Metab Res Rev,7:383–391.