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Creatine kinase and blood pressure in women with a history of early-onset preeclampsia

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ABSTRACT

Objectives: High plasma creatine kinase (CK) activity is associated with hypertension in the general and pregnant population. We hypothesize that women with a history of early-onset preeclampsia are prone to hypertension due to a high CK activity level.

Study design: Nine to 16 years after pregnancy, serum CK activity and blood pressure were measured in 117 women with a history of early-onset preeclampsia and 50 women with a history of an uncomplicated pregnancy.

Main outcome measures: CK activity levels of the two groups were compared using the Mann-Whitney *U* test. The association between CK activity and blood pressure was evaluated by means of multivariable regression analysis.

Results: There was no significant difference in median (interquartile range) CK activity between women with a history of early-onset preeclampsia and an uncomplicated pregnancy (59.00 [47.00–85.00] vs. 58.00 [46.50–75.25], respectively, p = 0.774). The association between CK and systolic blood pressure was significant in women with a pregnancy history of early-onset preeclampsia (regression coefficient [95% confidence interval]: 0.123 mmHg [0.020–0.226], p = 0.019), and a trend was found for diastolic blood pressure (p = 0.069). CK and blood pressure were not significantly associated in women with a history of an uncomplicated pregnancy.

Conclusions: Median CK did not significantly differ between the two groups. Serum CK activity was significantly associated with systolic blood pressure in women with a history of early-onset preeclampsia. These data suggest that CK is not a predominant factor in the increased risk of hypertension in women with a history of early-onset preeclampsia.

1. Introduction

Women with a history of preeclampsia have an increased risk of cardiovascular disease later in life [1,2]. Compared to women with an uncomplicated pregnancy, women with a history of preeclampsia have an almost fourfold risk of developing hypertension [3]. Moreover, cardiovascular events occur 8–10 years earlier than in women without a history of preeclampsia [3,4]. The risk of cardiovascular events is even more pronounced in women with early-onset preeclampsia, a condition that is diagnosed when women with preeclampsia deliver before 34 weeks of gestation [5]. Compared to 25% of the women with late-onset preeclampsia, 45% of women with early-onset preeclampsia developed hypertension already within the first years postpartum [6].

Despite these observations, the underlying mechanism of these long-term cardiovascular effects of preeclampsia still remains unclear.

In both the general and pregnant population, high plasma creatine kinase (CK) activity is associated with hypertension [7–9]. By facilitating vascular contractility and renal sodium retention, the adenosine tri-phosphate (ATP)-generating enzyme CK contributes to a higher blood pressure [10]. The different risks of hypertension between ethnic groups, especially in people of African ancestry, the subgroup known to have the highest CK activity levels, is considered indicative for the role

Abbreviations: CK, creatine kinase; ATP, adenosine tri-phosphate; NO, nitric oxide; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; IQR, interquartile range; SD, standard deviation; CI, confidence interval

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of CK in blood pressure [11,12]. Similarly suggestive for the role of CK is the racial difference in blood pressure observed during pregnancy. Women from African ancestry have higher rates of preeclampsia compared to Caucasian women [13], and this higher prevalence of preeclampsia is not completely attributable to the higher rate of chronic hypertension that is present in that population [14]. Furthermore, compared to Caucasian women, preeclampsia in women of African ancestry is more dominated by hypertension than liver enzymes abnormalities and a low platelet count [13]. Next to this, the effect of L-arginine supplementation is indicative for the role of CK in preeclampsia [15]. L-arginine is the precursor of creatine and nitric oxide (NO). A high CK activity raises the demand for creatine [16] and may reduce the rate of NO synthesis by lowering the available L-arginine. In a large randomized controlled trial of women at risk of preeclampsia, L-arginine supplementation decreased the risk of preeclampsia [15]. Supplementation of L-arginine may shift the vascular tone towards relaxation and lower the blood pressure by balancing the relative shortage of NO due to the high CK activity level. Lastly, ex vivo CK inhibition reduced vascular contractility of resistance arteries of pregnant women [12].

We hypothesize that high CK activity is a continuously present risk factor for hypertension throughout life, and that hypertension is more prevalent in women with a history of early-onset preeclampsia by the mechanism of high CK activity.

In this study, we first investigated whether the serum CK activity differs between women with a history of early-onset preeclampsia and women with a history of an uncomplicated pregnancy 9–16 years postpartum. Secondly, we assessed whether serum CK activity is associated with blood pressure in women with a history of early-onset preeclampsia.

2. Methods

2.1. Study population

This study is a sub study of the Hyprecare cohort, previously described in detail [17]. The objective of this study was to assess cardiovascular risk factors and established cardiovascular disease in the fifth decade of life, in women with a history of early-onset preeclampsia compared to women with a history of an uncomplicated pregnancy. Women were studied in this decade of life as it is suggested that screening in this time period would offer a window of opportunity to optimize preventive care before established cardiovascular disease have developed.

In brief, potentially eligible patients from two tertiary medical centers in the Netherlands were consecutively reviewed based on their obstetrical medical charts. Women with a medical history of early-onset preeclampsia were screened and all eligible women were asked to participate. Based on the International Society for the Study of Hypertension in Pregnancy 2001 criteria, early-onset preeclampsia was defined as delivery before 34 weeks' gestation, blood pressure $\geq$140/90 mmHg and new-onset proteinuria $\geq$300 mg/24 h in a previous normotensive woman [18].

The early-onset preeclampsia group was matched, based on maternal age (range $\pm$ 5 years) and date of delivery (range $\pm$ 1 year), with a group of women with a history of an uncomplicated pregnancy. Women were classified as having had an uncomplicated pregnancy when they gave birth after a normotensive pregnancy with absence of intrauterine growth restriction between 37 and 42 weeks of gestation.

Exclusion criteria for both women with a history of early-onset preeclampsia and uncomplicated pregnancy were: blood pressure measured in first trimester $\geq$140/90 mmHg, use of antihypertensive medication before index pregnancy; diabetes mellitus, gestational diabetes, cardiovascular diseases, or the use of cardiovascular related medication before index pregnancy; multiple pregnancy or congenital abnormalities in index pregnancy; pregnant at, or the last six months before, assessment; breastfeeding at time of assessment; and unreliable CK assessment due to a hemolytic or lipemic sample.

All participants gave birth between 1998 and 2005. Between 2014 and 2016, all participants that gave written informed consent were invited to the VU University Medical Center for a cardiovascular risk assessment. Of the 187 participants in the Hyprecare study, 167 gave consent to reuse their stored serum for sub-studies. The study was approved by the medical ethics committee of the VU University Medical Center in Amsterdam and locally by the hospital board of the Academic Medical Center Amsterdam (protocol approval: NL38972.029.12; Dutch trial registration: NTR5297).

2.2. Data collection

Before risk assessment, participants were asked to fill in a questionnaire in order to obtain information about demographic variables such as age, ethnicity and education, medical conditions and use of medication. Blood pressure was measured manually, twice in a sitting position. The average value of the two blood pressure measurements was calculated. Body height was measured using a wall-mounted stadiometer at 0.5 cm precision and weight was determined using a mechanical scale at 0.5 kg precision without shoes in light indoor clothing. Using a rigid tape-measure, the waist circumference was measured on uncovered skin at the slimmest point of the waist to the nearest 0.5 cm.

Hypertension was defined as either current use of antihypertensive medication and/or blood pressure $\geq$140/90 mmHg measured at risk assessment [19]. According to the Adult Treatment Panel III criteria, metabolic syndrome was diagnosed when three or more of the following characteristics were present: waist circumference > 88 cm, triglyceride levels $\geq$1.7 mmol/L, high-density lipoprotein cholesterol < 1.29 mmol/L, blood pressure $\geq$130/85 mmHg, and/or fasting glucose levels $\geq$5.7 mmol/L [20].

Venous blood samples were obtained and stored at minus 80 degrees Celsius. Total CK activity was analyzed using the stored serum by the 'NAC activated' method using the Cobas C8000 analyzer (Roche Diagnostics, Almere, the Netherlands) in the Laboratory for Clinical Chemistry of the VU University Medical Center in Amsterdam. With this method, total CK activity is indirectly determined by detecting an increase in nicotinamide adenine dinucleotide levels through an increase in ATP formation. The intra-assay and inter-assay coefficient of variation for CK were respectively 0.7% and 0.9%.

2.3. Statistical analysis

As this study is a sub study of the existing Hyprecare cohort, no sample size calculation was performed. Differences in demographic and clinical characteristic between women with a history of early-onset preeclampsia and women with an uncomplicated pregnancy were tested with the unpaired two sample *t*-test and Chi-square test when appropriate.

Serum CK activity levels of the two groups were compared using the Mann-Whitney *U* test. Differences in systolic blood pressure (SBP) and diastolic blood pressure (DBP) between women with a history of early-onset preeclampsia and an uncomplicated pregnancy were evaluated using the unpaired two sample *t*-test. Univariable and multivariable linear regression analyses were used to assess the association between CK activity and blood pressure in women with a history of early-onset preeclampsia and in women with a history of an uncomplicated pregnancy. Next to this stratified analysis, we evaluated this association in the whole cohort and we added the interaction term of pregnancy history and CK.

The following possible confounding variables were investigated using forward selection: ethnicity (Caucasian or non-Caucasian), age at time of cardiovascular risk assessment (in years), educational level (low: no schooling or elementary schooling only, lower vocational schooling or lower secondary schooling; intermediate: intermediate

Table 1
Demographic and clinical characteristics of participating women during index pregnancy and 9–16 years after index pregnancy by type of pregnancy history.

Characteristic		Early-onset preeclampsia (n = 117)	Uncomplicated pregnancy (n = 50)	p-value
During index pregnancy				
Age in years	mean ± SD	30.8 ± 5.0	32.5 ± 4.1	0.041
Primiparous	n (%)	90 (76.9)	27 (54.0)	0.003
At time of cardiovascular assessment 9–16 years after index pregnancy				
Age in years	mean ± SD	44.0 ± 5.6	46.8 ± 4.8	0.002
Ethnicity				
Caucasian	n (%)	104 (88.9)	44 (88.0)	0.868
Non-Caucasian	n (%)	13 (11.1)	6 (12.0)	
Educational level				0.068
Low	n (%)	28 (23.9)	5 (10.0)	
Intermediate	n (%)	43 (36.8)	18 (36.0)	
High	n (%)	45 (38.8)	27 (54.0)	
Current hypertension	n (%)	46 (39.3)	6 (12.0)	< 0.001
BMI in kg/m^2	mean ± SD	26.6 ± 5.2	24.1 ± 3.8	0.002
Metabolic syndrome	n (%)	20 (17.1)	1 (2.0)	0.007
Family history of hypertension	n (%)	81 (69.2)	31 (62.0)	0.286
Alcohol use				0.451
No	n (%)	42 (35.9)	14 (28.0)	
< 14 units per week	n (%)	73 (62.4)	34 (68.0)	
≥14 units per week	n (%)	2 (1.7)	2(4.0)	

Abbreviations: n: number; SD: standard deviation; BMI: body mass index.

vocational schooling or intermediate/higher secondary schooling; high: higher vocational schooling or university), parity (number of previous deliveries), metabolic syndrome (yes or no) and alcohol consumption (no, < 14 units per week or ≥14 units per week). A change-in-estimate of ≥10% of the unadjusted exposure-outcome effect was considered significant confounding.

In all the analyses regarding blood pressure, women that used antihypertensive medication during cardiovascular risk assessment were excluded.

A p-value < 0.05 was considered statistically significant. Statistical analyses were performed with SPSS 22 software (IBM Corp, Armonk, NY).

3. Results

3.1. Study population

Of the 167 participating women, 117 had a history of early-onset preeclampsia and 50 a history of an uncomplicated pregnancy. In Table 1 demographic and clinical characteristics are summarized. Women with a history of early-onset preeclampsia were relatively younger (p = 0.041) and more often primiparous (p = 0.003) at index pregnancy. Nine to 16 years after index pregnancy, women with a history of early-onset preeclampsia were younger (p = 0.002), had a higher body mass index (BMI) (p = 0.002), more often hypertension (p < 0.001) and metabolic syndrome (p = 0.007) than the women with a history of an uncomplicated pregnancy (Table 1).

3.2. Serum CK activity

Median serum CK activity levels did not differ significantly between women with a history of early-onset preeclampsia and in women with an uncomplicated pregnancy 9–16 years after index pregnancy (59.00 [interquartile range (IQR) 47.00–85.00] vs. 58.00 [IQR 46.50–75.25], respectively, p = 0.774).

Table 2
Association between creatine kinase and blood pressure.

Outcome	Regression coefficient[a]	95% confidence interval	Adjusted for[b]	p-value
Early onset preeclampsia (n = 95)				
SBP	0.123	(0.020; 0.226)	None	0.019
DBP	0.052	(−0.004; 0.108)	None	0.069
Uncomplicated pregnancy (n = 50)				
SBP	0.011	(−0.060; 0.091)	ethnicity, metabolic syndrome, alcohol use	0.784
DBP	0.006	(−0.033; 0.044)	metabolic syndrome, alcohol use	0.776

Abbreviations: n: number; SBP: systolic blood pressure; DPB: diastolic blood pressure; none: none of the confounders remained significant.

[a] Showing regression coefficients of blood pressure in mmHg per 1-unit serum CK activity (IU/L) increase.

[b] Adjusted for the confounders identified as significant using forward selection (see methods).

3.3. Association between serum CK activity and blood pressure

Twenty-two subjects, all from the early-onset preeclampsia group, that used antihypertensive medication were excluded from the analyses on blood pressure.

Nine to 16 years after the index pregnancy, the mean SBP and DBP of women with a history of early-onset preeclampsia were 125.2 (SD ± 18.8) and 81.0 (SD ± 10.2) mmHg, respectively. The mean SBP and DBP of women with a history of an uncomplicated pregnancy were 114.6 (SD ± 17.2) and 73.3 (SD ± 9.5) mmHg, respectively. Both the mean SBP and mean DBP differed significantly between the two groups (p = 0.001 and p < 0.001 respectively).

In the pregnancy-history specific analyses, serum CK activity and SBP were significantly associated in women with a pregnancy history of early-onset preeclampsia (regression coefficient 0.123 mmHg [95% confidence interval (CI) 0.020 to 0.226], p = 0.019), but not significantly associated in women with a history of an uncomplicated pregnancy (regression coefficient 0.011 mmHg [95% CI −0.069 to 0.091], p = 0.784) (Table 2). For the association between CK and DBP, a trend was found in women with a history of early-onset preeclampsia (regression coefficient 0.052 mmHg [95% CI −0.004 to 0.108], p = 0.069), and no association was found in women with a history of an uncomplicated pregnancy.

Studying the whole study population, the multivariable analysis showed a significant association between CK activity and SBP (regression coefficient 0.071 mmHg [95% CI 0.011 to 0.131], p = 0.020), and a trend for CK and DBP (regression coefficient 0.025 mmHg [95% CI −0.006 to 0.055], p = 0.100). However, the test for interaction of CK and pregnancy history was not significant in the association between CK and SBP (p = 0.159).

4. Discussion

We found that women with a history of early-onset preeclampsia and women with a history of an uncomplicated pregnancy, had no significantly different serum CK activity. Serum CK activity was associated with systolic blood pressure 9–16 years postpartum in women with a history of early-onset preeclampsia. In these women, systolic blood pressure increased 0.123 mmHg (CI 0.020–0.226, p = 0.019) per 1-unit serum CK activity (IU/L). Likewise, a 100-unit increase in the CK activity would correspond to a 12.3 mmHg increase in systolic blood pressure. Putting this into a clinical perspective, a difference of 20 mmHg in systolic blood pressure at age 40–69 years is associated with a twofold increase in cardiovascular death rate [21].

As described earlier by Sattar et al., pregnancy can be regarded as a stress test for cardiovascular disease later in life [22]. In line with this

theory, the hypertension prone nature associated with high CK would first become apparent during pregnancy as a hypertensive pregnancy disorder, and later in life in its associated increased risk of hypertension.

4.1. Strengths and limitations

Serum CK activity was not significantly associated with systolic nor diastolic blood pressure in women with a history of an uncomplicated pregnancy. However, this non-significance could be due to the small sample size of the subgroup. Larger studies are needed to clarify the association between CK and blood pressure in women with a history of an uncomplicated pregnancy. The strength of this cohort lies in its large number of women with a history of early-onset preeclampsia, which is a relatively rare and severe disease, who underwent cardiovascular risk assessment in their fifth decade of life.

This cohort mainly concerns Caucasian women (> 80%), which most likely explains the narrow range of the serum CK activity (19–494 IU/L) compared to two previous multi-ethnic cohorts in the general population (14–5783 IU/L and 10–15941 IU/L) [7,8]. It is possible that in a multi-ethnic study most likely with a wider range of CK, a significant difference in CK activity between women with a history of preeclampsia and a normotensive pregnancy would be found.

Exercise is known to be a common cause of elevated serum CK activity levels [23]. In this study, participants were not asked to refrain from exercise the days prior to blood drawl. Therefore, it cannot be excluded that the higher CK activity levels found in certain participants reflects recent muscle damage rather than being a marker of steady state tissue CK activity.

Regarding blood pressure analyses, excluding women that used antihypertensive medication results in a more reliable estimate of the influence of CK on blood pressure. However, not finding an effect of CK may be the result of excluding the highest blood pressures needing medical intervention. Furthermore, multiple reports suggests that correction for BMI leads to an overadjustment of the effect of CK on blood pressure [9,24,25]. CK is independently associated with BMI and waist-to-hip ratio [26]. A high CK is considered a reflection of a type II skeletal muscle fibre predominance, which is associated with obesity [27,28]. In this study we did not correct for BMI in the analyses, as BMI is seen as a mediator and thus in the causal chain of CK and blood pressure.

The limitations as described by Bokslag et al. [17] also apply to this sub study. Measuring blood pressure twice during one visit instead of in multiple visits might have led to higher blood pressures in the study sample. The response rates were low; 53% in the early-onset preeclampsia group and 26% in the uncomplicated pregnancy group respectively. Hereby, selection bias could have occurred, if assumed that women with the most severe disease in pregnancy were willing to participate as they are known to have a higher cardiovascular risk. The same selection bias could have occurred with the inclusion of women with a relatively high risk to experience cardiovascular disease.

Inherent to the observational nature of this study, the association found between CK and blood pressure does not prove causality. Furthermore, no studies have been performed treating hypertension by altering the CK metabolism. In other words, this study confirms the association between CK and blood pressure in women with a history of early-onset preeclampsia, but evidence supporting the role of CK in the pathophysiology of hypertension is still lacking.

4.2. Clinical implication

As high CK could pose persistent hypertension burden it could have a role in identifying women with an increased risk for hypertension and cardiovascular disease. More frequent blood pressure screening in individuals with a high serum CK activity could be advocated. However, its role as a potential predictor has not been addressed in this study. Next to this, it is unclear whether this test might add significantly to blood pressure screening based on obstetric and medical history alone. Given the fact there was no significant difference in serum CK activity between women with a history of early-onset preeclampsia and an uncomplicated pregnancy, we assume that CK will not be a eligible biomarker.

5. Conclusion

Serum CK activity was not different between women with a history of early-onset preeclampsia compared to women with history of an uncomplicated pregnancy. Yet, serum CK activity and systolic blood pressure 9–16 years postpartum were significantly associated in women with a history of early-onset preeclampsia.

Disclosures/Conflict of interest

There are no conflicts of interest or disclosures.

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References

[1] F. Charlton, J. Tooher, K.A. Rye, A. Hennessy, Cardiovascular risk, lipids and pregnancy: preeclampsia and the risk of later life cardiovascular disease, Heart Lung Circ. 23 (2014) 203–212, https://doi.org/10.1016/j.hlc.2013.10.087.
[2] G. Osol, I. Bernstein, Preeclampsia and maternal cardiovascular disease: consequence or predisposition? J. Vasc. Res. 51 (2014) 290–304, https://doi.org/10.1159/000367627.
[3] G.A. Zoet, M.P.H. Koster, B.K. Velthuis, C.J.M. De Groot, A.H.E.M. Maas, B.C.J.M. Fauser, A. Franx, B.B. Van Rijn, Determinants of future cardiovascular health in women with a history of preeclampsia, Maturitas 82 (2015) 153–161, https://doi.org/10.1016/j.maturitas.2015.07.004.
[4] B.B. Van Rijn, K.Y. Heida, J.H. Veerbeek, M.P. Koster, Y.T. Van Der Schouw, M.L. Bots, A. Franx, Pregnancy as a cardiovascular challenge test: evaluation of hypertension and diabetes in pregnancy as predictors for cardiovascular disease among 15,175 women aged 49–70 years, Reprod. Sci. 20 (2013) 105A, https://doi.org/10.1177/1933719113482088.
[5] J.T. Drost, G. Arpaci, J.P. Ottervanger, M.J. De Boer, J. Van Eyck, Y.T. Van Der Schouw, A.H. Maas, Cardiovascular risk factors in women 10 years post early preeclampsia: the Preeclampsia Risk EValuation in FEMales study (PREVFEM), Eur. J. Prev. Cardiol. 19 (2012) 1138–1144, https://doi.org/10.1177/1741826711421079.
[6] J.H.W. Veerbeek, W. Hermes, A.Y. Breimer, B.B. Van Rijn, S.V. Koenen, B.W. Mol, A. Franx, C.J.M. De Groot, M.P.H. Koster, Cardiovascular disease risk factors after early-onset preeclampsia, late-onset preeclampsia, and pregnancy-induced hypertension, Hypertension 65 (2015) 600–606, https://doi.org/10.1161/HYPERTENSIONAHA.114.04850.
[7] L.M. Brewster, G. Mairuhu, N.R. Bindraban, R.P. Koopmans, J.F. Clark, G.A. Van Montfrans, Creatine kinase activity is associated with blood pressure, Circulation 114 (2006) 2034–2039, https://doi.org/10.1161/CIRCULATIONAHA.105.584490.
[8] S.H. Johnsen, H. Lilleng, T. Wilsgaard, S.I. Bekkelund, Creatine kinase activity and blood pressure in a normal population: the Tromsø study, J. Hypertens. 29 (2011) 36–42, https://doi.org/10.1097/HJH.0b013e32834068e0.
[9] D.L. Horjus, A. Bokslag, B.A. Hutten, B.J.H. Van den Born, S. Middeldorp, T.G.M. Vrijkotte, Creatine kinase is associated with blood pressure during pregnancy, J. Hypertens. (2018), https://doi.org/10.1097/HJH.0000000000001900 in press.
[10] T.G. Pickering, Muscular hypertension: is creatine kinaseresponsible for hypertension in blacks? J. Clin. Hypertens. 10 (2008) 73–76, https://doi.org/10.1111/j.1524-6175.2007.07846.x.
[11] L.M. Brewster, G. Mairuhu, A. Sturk, G.A. van Montfrans, Distribution of creatine kinase in the general population: implications for statin therapy, Am. Heart J. 154 (2007) 655–661, https://doi.org/10.1016/j.ahj.2007.06.008.
[12] L.M. Brewster, Z. Taherzadeh, S. Volger, J.F. Clark, T. Rolf, H. Wolf, E. Vanbavel, G.A. van Montfrans, Ethnic differences in resistance artery contractility of normotensive pregnant women, Am. J. Physiol. Heart Circ. Physiol. 299 (2010)

H431–H436, https://doi.org/10.1152/ajpheart.00919.2009.
[13] A.A. Goodwin, B.M. Mercer, Does maternal race or ethnicity affect the expression of severe preeclampsia? Am. J. Obstet. Gynecol. 193 (2005) 973–978, https://doi.org/10.1016/j.ajog.2005.05.047.
[14] A.S. Bryant, E.W. Seely, A. Cohen, E. Lieberman, Patterns of pregnancy-related hypertension in Black and White women, Hypertens. Pregnancy 24 (2005) 281–290, https://doi.org/10.1080/10641950500281134.
[15] T. Dorniak-Wall, R.M. Grivell, G.A. Dekker, W. Hague, J.M. Dodd, The role of L-arginine in the prevention and treatment of pre-eclampsia: a systematic review of randomised trials, J. Hum. Hypertens. 28 (2014) 230–235, https://doi.org/10.1038/jhh.2013.100.
[16] M.R. Iyengar, Creatine kinase as an intracellular regulator, J. Muscle Res. Cell Motil. 5 (1984) 527–534, https://doi.org/10.1007/BF00713259.
[17] A. Bokslag, P.W. Teunissen, C. Franssen, F. van Kesteren, O. Kamp, W. Ganzevoort, W.J. Paulus, C.J.M. de Groot, Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life, Am. J. Obstet. Gynecol. 216 (2017) 523.e1–523.e7, https://doi.org/10.1016/j.ajog.2017.02.015.
[18] M.A. Brown, M.D. Lindheimer, M. de Swiet, A. Van Assche, J.M. Moutquin, The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the International Society for the Study of Hypertension in Pregnancy (ISSHP), Hypertens. Pregnancy 20 (2001) IX–XIV, https://doi.org/10.1081/PRG-100104165.
[19] A.V. Chobanian, G.L. Bakris, H.R. Black, W.C. Cushman, L.A. Green, J.L. Izzo, D.W. Jones, B.J. Materson, S. Oparil, J.T. Wright, E.J. Roccella, The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report, JAMA 289 (2003) 2560–2572, https://doi.org/10.1001/jama.289.19.2560.
[20] Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, Executive summary of the third report of the National Cholesterol Education Program (NCEP), JAMA 285 (2001) 2486–2497, https://doi.org/10.1001/jama.285.19.2486.
[21] S. Lewington, R. Clarke, N. Qizilbash, R. Peto, R. Collins, Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies, Lancet 360 (2002) 1903–1913, https://doi.org/10.1016/S0140-6736(02)11911-8.
[22] N. Sattar, I.A. Greer, Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? BMJ 325 (2002) 157–160, https://doi.org/10.1136/bmj.325.7356.157.
[23] G.A. Nicholson, J.G. McLeod, G. Morgan, M. Meerkin, J. Cowan, A. Bretag, D. Graham, G. Hill, E. Robertson, L. Sheffield, Variable distributions of serum creatine kinase reference values. Relationship to exercise activity, J. Neurol. Sci. 71 (1985) 233–245, https://doi.org/10.1016/0022-510X(85)90062-0.
[24] S.H. Johnsen, H. Lilleng, S.I. Bekkelund, Creatine kinase as predictor of blood pressure and hypertension. Is it all about body mass index? A follow-up study of 250 patients, J. Clin. Hypertens. 16 (2014) 820–826, https://doi.org/10.1111/jch.12422.
[25] Y.C. Haan, G.A. van Montfrans, L.M. Brewster, The high creatine kinase phenotype is hypertension- and obesity-prone, 322–322, J. Clin. Hypertens. 17 (2015), https://doi.org/10.1111/jch.12490.
[26] Y.C. Haan, I. Oudman, F.S. Diemer, F.A. Karamat, I.G. van Valkengoed, G.A. van Montfrans, L.M. Brewster, Creatine kinase as a marker of obesity in a multi-ethnic population, Mol. Cell. Endocrinol. 442 (2017) 24–31, https://doi.org/10.1016/j.mce.2016.11.022.
[27] M.S. Hickey, J.O. Carey, J.L. Azevedo, J.A. Houmard, W.J. Pories, R.G. Israel, G.L. Dohm, Skeletal muscle fiber composition is related to adiposity and in vitro glucose transport rate in humans, Am. J. Physiol. Metab. 268 (1995) E453–E457, https://doi.org/10.1152/ajpendo.1995.268.3.E453.
[28] C.J. Tanner, H.A. Barakat, G.L. Dohm, W.J. Pories, K.G. MacDonald, P.R.G. Cunningham, M.S. Swanson, J.A. Houmard, Muscle fiber type is associated with obesity and weight loss, Am. J. Physiol. – Endocrinol. Metab. 282 (2002) E1191–E1196, https://doi.org/10.1152/ajpendo.00416.2001.