Mini Review

Glucocorticoid excess and disturbed hemodynamics in advanced age: the extent to which soy isoflavones may be beneficial

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Abstract. Advanced age is often accompanied by glucocorticoid excess which contributes to the pathogenesis of the metabolic syndrome associated with some hemodynamic disorders. Impaired central regulation of stress hormones secretion and increased glucocorticoids/adrenal androgens ratio trigger hyperglycemia, elevated blood lipids and visceral fat accumulation, associated with hypertension and increased blood viscosity, all of which represent cardiovascular morbidity factors in this age. Finding the adequate therapeutic solutions is set as an imperative in the treatment of listed symptoms. Biologically active soy isoflavones, exhibiting estrogen- and membrane-receptor agonistic/antagonistic activity, and antioxidative and tyrosine kinase/steroidogenic enzyme inhibiting effects, appear as alternative therapeutics for various ageing-related diseases. It has been shown that soy isoflavones reduce some of the listed risk factors, while affecting the hemodynamic group of cardiovascular parameters directly, as well as indirectly *via* endocrine perturbations. Soy isoflavones may reverse the glucocorticoids/adrenal androgens ratio, lower serum cholesterol, slow the development of atherosclerotic plaque formation, inhibit platelet aggregation, increase cardiac contractility, but they may have diverse effects on blood viscosity and may increase triglyceride levels. Herein, we present the projection of soy isoflavones-based therapy of glucocorticoid excess and disturbed hemodynamics in advanced age, concluding that although promising, it requires the impartial approach and certain precautions.

Key words: Advanced age — Glucocorticoids — Cardiovascular parameters — Hemodynamics — Soy isoflavones
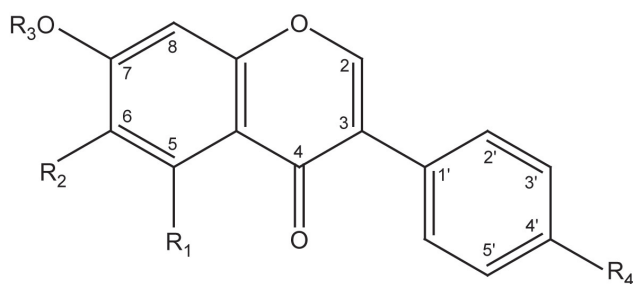
Abbreviations: CO, cardiac output; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone sulphate; HPA, hypothalamo-pituitary-adrenal; 3β-HSD, 3-β-hydroxysteroid dehydrogenase; LDL, low-density lipoprotein; MetS, metabolic syndrome; P450c21, cytochrome P-450 21-hydroxylase; PPAR, peroxisome-proliferator activating receptor.

Impairment of central regulation of glucocorticoid secretion with aging

The hypothalamo-pituitary-adrenal (HPA) system is involved in stress response and represents the central point of the endocrine, nervous and immune systems integration (Ferrari et al. 2001). Endogenous glucocorticoids are

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produced in the adrenal glands cortex and, in a circadian manner, secreted into the circulation, showing a tendency to elevate in response to stress and disease. It has been proposed that increased HPA system activity followed by elevated glucocorticoids may contribute to lower bone mineral density (Greendale at al. 1999), and to the pathogenesis of the metabolic syndrome (MetS) characterized by insulin resistance coherent with hyperglycemia and "bad" profile of blood lipids, visceral fat accumulation and hypertension (Obunai et al. 2007; Ørgaard and Jensen 2008; Anagnosits et al. 2009). Advanced age is followed by synaptic/neuronal loss and impaired central regulation of adrenocortical secretion,

Isoflavone	R_1	R_2	R_3	R_4
Genistein	OH	H	H	OH
Daidzein	H	H	H	OH
Glycitein	H	OCH_3	H	OH
Formononetin	H	H	H	OCH_3
Biochanin A	OH	H	H	OCH_3
Genistin	OH	H	Glu	OH
Daidzin	H	H	Glu	OH
Glycitin	H	OCH_3	Glu	OH
Ononin	H	H	Glu	OCH_3
Sissotrin	OH	H	Glu	OCH_3

Figure 1. The general formula of soy isoflavones and related glucosides.

leading to a significant increase in the glucocorticoids/adrenal androgens ratio (Ferrari et al. 2001; Nichols et al. 2001; Rosenzweig and Barnes 2003) which is consistent with the large prevalence of MetS at this age (Akbaraly et al. 2011). And *vice versa*, there is evidence that high levels of glucocorticoids contribute to degenerative changes in certain brain regions and to cognitive disorders during aging in some individuals (Nichols et al. 2001). Finally, age-related decrease of adrenal androgens secretion results in the loss of anti-glucocorticoid protection and leads to enhanced neurotoxicity and structural damage in the hippocampus (McEwen 1999; Ferrari et al. 2001).

Altered hemodynamics in advanced age

Various parameters of hemodynamics or "blood movement", including cardiac output (CO), circulating blood volume, vascular diameter/resistance and blood viscosity, all influencing blood pressure, show a tendency to deteriorate during ageing. Such pathological changes are further pronounced in conditions like obesity, hyperlipidemia and atherosclerosis, which are inherent to MetS and advanced age. In obese patients a high prevalence of hypertension has been suggested (Zhang and Reisin 2000) associated with increased CO and peripheral vascular resistance (Redon

2001). These changes lead to left ventricular hypertrophy, which provides the basis for the development of cardiac arrhythmias and heart failure (Zhang and Reisin 2000). Atherosclerosis is a complex multifactorial disease whose pathogenesis involves smooth muscle-cell proliferation, lipid deposition, thrombosis and calcification (Wilcox and Blumenthal 1995). Atherosclerotic plaques *de facto* represent mechanical barriers to blood flow, significantly disrupting the hemodynamics. The fluidity of erythrocyte membrane, representing the feature that defines erythrocyte deformability/blood viscosity (Cartwright et al. 1985; Zicha et al. 1999), is compromised in hypertension and atherosclerosis. Namely, membrane fluidity of erythrocytes is significantly lower in both spontaneously hypertensive rats and patients with essential hypertension, in comparison to normotensive controls (Tsuda et al. 1987; Tsuda 2010). It was observed that low erythrocyte membrane fluidity negatively affects erythrocyte deformability/blood viscosity (Cartwright et al. 1985; Heilmann et al. 1994). Finally, glucocorticoid excess may also disturb hemodynamics in advanced age, by contributing to the development of some MetS symptoms (Yanovski and Cutler 1994; Friedman et al. 1996; Anagnostis et al. 2009).

Soy isoflavones: the extent of potential benefits

General considerations

Humans are introduced to biologically active isoflavones *via* diet, primarily soy-derived foods, and dietary supplements which contain high levels of these estrogen-like diphenolic compounds (Price and Fenwick 1985; Adlercreutz and Mazur 1997). Weak estrogenic and antiestrogenic activity was observed following soy isoflavone application, both *in vivo* and *in vitro* (Price and Fenwick 1985). In addition, soy isoflavones exhibit strong antioxidative activity (Benassayag et al. 2002) as well as tyrosine kinase inhibiting effects (Akiyama et al. 1987).

Elaboration of soy isoflavones effects on glycemic status indicates the distinction between *in vitro* and *in vivo* data. Soy isoflavone genistein is able to enhance insulin secretion in some cell lines as well as in isolated mouse and rat pancreatic islets (Sorenson et al. 1994; Jonas et al. 1995; Szkudelska and Nogowski 2007). The observed effect is shown to be estrogen receptor- and tyrosine kinase-independent. However, it was found that genisteins' insulinotropic activity, in cell lines and pancreatic islets, is based on cAMP increase and protein kinase A activation (Liu et al. 2006; Szkudelska and Nogowski 2007). Contrary to the *in vitro* observations, results of *in vivo* studies indicate that genistein does not increase blood insulin. Namely, it causes the lowering of circulating insulin in rats and post-menopausal women (Szkudelska et al. 2003;
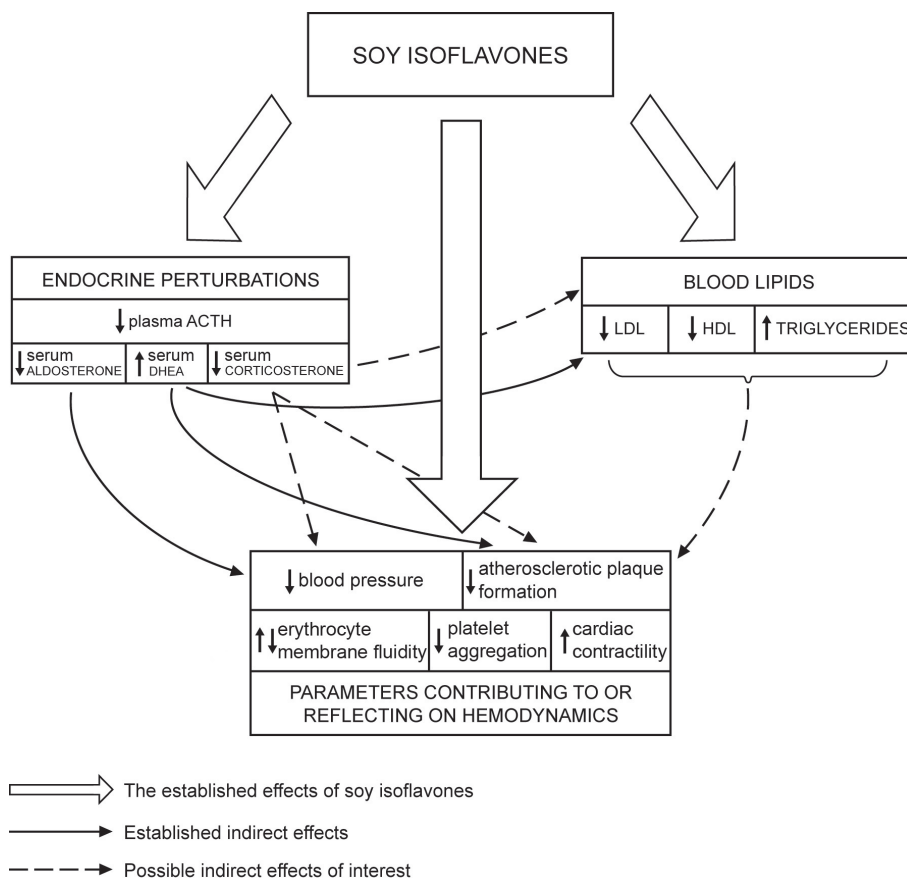
Figure 2. The effects of soy isoflavones on hemodynamics, endocrine perturbations, and blood lipids. ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Cheng et al. 2004; Lephart et al. 2004). Also, it should be mentioned that genistein, in some animal models, reduces lipoprotein lipase gene expression in adipose tissue, which contributes to diminished lipid uptake by fat cells and to the prominent anti-obesity effects (Naaz et al. 2003).

A significant amount of research interest has been focused on the effectiveness of soy isoflavones as natural therapeutics for cardiovascular problems. It was suggested that estrogens reduce morbidity related to coronary artery disease in postmenopausal women (Sullivan and Fowlkes 1996). Unfortunately, later on it was observed that the application of estrogens in parallel may increase the risk for thromboembolism or cancer development (Grady et al. 2000; Fournier et al. 2003), which dampened the enthusiasm for their application. Early studies on soy isoflavones, introduced as an alternative to estrogens, suggested that they may decrease the level of cholesterol in serum (Setchell 1985), as well as slow down the atherosclerotic plaques formation by inhibiting cell adhesion and by altering the activity of specific growth factors (Raines and Ross 1995). Also, it was shown that acute and 2-day treatment with

genistein increases cardiac contractility in isolated working rat hearts (Al-Nakkash et al. 2009), suggesting effects of genistein on CO. Our results on middle-aged male rats indicate that genistein and the related compound – daidzein decrease serum cholesterol, but increase the triglycerides level (Šošić-Jurjević et al. 2007). The up-regulation of low-density lipoprotein (LDL) receptors and the inhibition of endogenous cholesterol synthesis are the most probable explanations for the observed effects (Tham et al. 1998). Demarcation between the soy isoflavone and soy protein effects *per se* in the lipid profile is not entirely clear. Some data suggest that soy proteins are principally responsible for the blood lipid-lowering effects of soy (Wagner et al. 2000), *via* up-regulation of the expression of hepatic thyroid hormone receptor β1 involved in cholesterol metabolism (Xiao et al. 2004). The fact is that the removal of the isoflavone fraction from soy protein results in the loss of its beneficial effect in hypercholesterolemic subjects (Gardner et al. 2001). It has been proposed that soy isoflavones exert their hypocholesterolemic and anti-atherosclerotic activity by acting as peroxisome-proliferator activating receptor (PPAR)

agonists (Mezei et al. 2003). PPAR are nuclear receptors that regulate the transcription of genes involved in lipid metabolism within the cell. Finally, it was suggested that genistein and daidzein could inhibit platelet aggregation by acting as thromboxane A2 membrane receptor antagonists (Nakashima et al. 1991), which may prevent the thrombus formation.

Effects on corticosteroid secretion and potential implications

Some studies suggest that soy isoflavones prevent chemically-induced hippocampal neuronal loss (Azcoitia et al. 2006). Presumably, given the importance of hippocampus in the regulation of corticosteroid secretion, as well as its deterioration during ageing, soy isoflavones may have the potential to prevent glucocorticoid excess in advanced age. Genistein and daidzein are the prominent inhibitors of 3β-HSD and cytochrome P-450 21-hydroxylase (P450c21) enzymes, thus directly affecting adrenocortical steroidogenesis (Ohno et al. 2002; 2003). The results from different animal studies suggest that subcutaneous administration of various doses of genistein (3 nmol/100 g/day– 0.11 mmol/kg/day) decreases the circulating levels of both adrenocorticotropic hormone (ACTH) and corticosterone (Malendowicz et al. 2006; Ajdžanović et al. 2009a; Milošević et al. 2009). In addition, genistein causes the shunting of steroid metabolic pathways in the adrenals by favoring dehydroepiandrosterone (DHEA) and inhibiting cortisol/corticosterone and aldosterone production *in vitro*, as well as *in vivo* in an animal model of the andropause (Mesiano et al. 1999; Sirianni et al. 2001; Ajdžanović et al. 2009b). Daidzein, which comprises a slight but very important structural difference when compared to genistein (the lack of C5 hydroxyl group), applied in a dose of 0.12 mmol/kg/day, also lowers ACTH and corticosterone levels in andropausal rats (Ajdžanović et al. 2011b). The doses of genistein or daidzein, employed in the studies of andropause, were chosen to mimic human exposure to elevated concentrations of isoflavones when nutritional supplements are used for therapeutic purposes (Doerge and Sheehan 2002). It is important to note that soy isoflavones alter adrenocortical steroid production without affecting the expression of steroidogenic enzymes, most likely by modulating steroidogenic enzyme and tyrosine kinase activities (Bodart et al. 1995; Mesiano et al. 1999). Considering previously elaborated roles of glucocorticoids in MetS and hemodynamic alterations, their decrease following soy isoflavone application may represent a significant therapeutical goal. It is noteworthy that angiotensin-converting enzyme inhibitors, which block the renin-angiotensin-aldosterone system involved in the pathogenesis of hypertension and heart failure, have been recognized as a therapy of choice in hypertension and heart failure (Verdecchia et al. 2012). The well established

role of genistein in the inhibition of aldosterone synthesis (Sirianni et al. 2001; Ajdžanović et al. 2009b) reinforces the idea of the application of soy isoflavones in hypertension treatment. Pertinent to this, we have observed a several-fold increase in DHEA levels in middle-aged male rats following the treatment with genistein (Ajdžanović et al. 2009b). Some prospective population-based studies suggest that androgens are not significantly associated with the cardio-vascular risks (Barrett-Connor and Khaw 1988), but on the other hand have been reported to elevate blood pressure in spontaneously hypertensive rats (Martin et al. 2005). High adrenal androgens, DHEA and dehydroepiandrosterone sulphate (DHEAS), have been suggested to be cardioprotective, while DHEA supplementation was reported to reduce cholesterol levels and atherosclerotic plaque formation in humans and animal models (Khaw 1996). Also, some clinical studies indicate that several months of treatment with DHEA is safe for older women when it comes to cardiovascular risk factors (Boxer et al. 2010). Conversely, the results on DHEAS showed increased cardiovascular risks in a population with "bad life habits" (Hautanen et al. 1994). Hence, further research addressing DHEA(S) clinical potentials as well as their roles in the effects of soy isoflavones remains a challenge. Certainly, in a broader context of the therapeutic strategies consideration, some isoflavone antiandrogen effects (Lund et al. 2004, 2011) and the potential implications on cardiovascular health should not be disregarded.

Direct effects on hemodynamics

A randomized controlled trial showed that increased dietary soy intake lowers blood pressure in hypertensives independently of age, gender, and weight variations, alcohol intake, or urinary sodium and potassium levels (Burke et al. 2001). Another study showed that long-term soy supplementation in male and post-menopausal female subjects significantly reduced systolic, diastolic and mean arterial pressure, which may be attributed, at least partially, to the observed decrease in peripheral vascular resistance (Teede et al. 2001). However, at the same time there were some indications of adverse cardiovascular effects. In a subsequent study, Teede's group found that the application of soy isoflavone formononetin (a precursor of daidzein) in a similar group of subjects resulted in the reduction of total peripheral resistance (Teede et al. 2003). When it comes to the soy isoflavones-caused vasomotor effects, it seems that endothelium-dependent, as well as, endothelium-independent mechanisms are operative. Various animal and human studies suggest that soy isoflavones-influenced vasorelaxation is nitric oxide (NO)-dependent (Vera et al. 2005; Hall et al. 2008), although, it has been observed that a soy rich diet does not affect the level of endothelial NO synthase (Schreihofer et al. 2010). On the

other hand, daidzein was reported to cause vasorelaxation by significantly increasing the conductance of Ca^{2+}-activated K^+ channels in vascular smooth muscle cells (Zhang et al. 2010). The effects on peripheral circulation could be explained by the influence of soy isoflavones on erythrocyte membrane fluidity, which affects erythrocyte deformability/blood viscosity. We have shown recently that daidzein provokes a significant increase in the fluidity of deeper layers of erythrocyte membrane (Ajdžanović et al. 2010). In contrast, the more hydrophilic genistein induced a decrease in erythrocyte membrane fluidity near the hydrophilic surface (Ajdžanović et al. 2010). Clearly, the number and polarity of functional groups in soy isoflavones and their glucosilated forms determinate the positioning of these compounds in the erythrocyte membrane, which reflects on the membrane molecular order and, consequently, on its fluidity. Isoflavone β-glucosides-rich soy extract acted in a similar fashion to genistein on the erythrocyte membrane fluidity, which may have negative implications on erythrocyte rheologic behavior/blood viscosity (Ajdžanović et al. 2011a). It is known that the isoflavone content and profiles in soy may vary considerably in relation to soy variety and geographic and environmental conditions, as well as to the mode of industrial processing (Cassidy et al. 2000; De Lima Toccafondo Vieira et al. 2008), which may account for the inconsistent results of *in vivo* studies. This implies that soy isoflavone extracts should not be used as an end-product applicable in human treatment, but that more effort should be invested in finding specific component(s) responsible for beneficial, as well as for adverse effects. According to the available data, soy products showing high levels of daidzein and low levels of genistein and isoflavone β-glucosides could be a more beneficial component of the diet of patients with cardiovascular diseases.

Conclusion

Soy isoflavones exert effects on the hemodynamics directly, as well as indirectly, *via* endocrine perturbations. It was shown that soy isoflavones may reverse the glucocorticoids/ adrenal androgens ratio, frequently disturbed in advanced age. The algorithm of soy isoflavones effects in this field, besides beneficial, comprises some with the negative sign (e.g. increased triglyceride levels) as well as effects with ambiguous implications (in the domain of androgens). Differences between the effects during developmental *vs.* advanced phases of hypertension and the functional role of soy isoflavones chemical structure should particularly be taken into account. When considering the results of *in vitro* and animal studies, and comparing them with those in human studies, it should be noted that the differences exist (e.g. the effects of genistein on insulin secretion), and that

certain, physiologically relevant, metabolic conversions of soy isoflavones do not affect the entire human population (e.g. daidzein conversion to equol occurs only in 30–40% of humans). It can be concluded that advantages in soy isoflavones-based therapy of glucocorticoid excess and disturbed hemodynamics in advanced age exist, but the development of potential therapeutics requires a balanced and impartial approach.

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