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Review

Is the metabolic syndrome a useful clinical concept in dogs? A review of the evidence

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ABSTRACT

The metabolic syndrome is a set of risk factors for the development of type 2 diabetes, atherosclerosis, coronary heart disease and stroke in human beings. The term has recently been applied to dogs that exhibit components of the human metabolic syndrome, specifically visceral obesity, hypercholesterolaemia, hypertriglyceridaemia, hypertension and fasting hyperglycaemia. Obese dogs, like obese humans, are known to develop resistance to the glucose-lowering effects of insulin, and develop increased circulating concentrations of triglycerides, cholesterol and blood pressure. Unlike humans, however, obese dogs do not develop fasting hyperglycaemia or atherogenic hyperlipidaemia. Importantly, there is no evidence that dogs develop type 2 diabetes. Atherosclerosis, coronary heart disease and stroke are rare and not known to be associated with obesity in dogs. On the basis of current knowledge, the use of the term 'metabolic syndrome' in dogs does not appear to have merit.

Introduction

The epidemic of obesity in dogs parallels that in humans (German, 2006b). Obesity has adverse effects on the quality of life (German et al., 2011) and health (German, 2006a) of dogs. In humans, one important obesity-associated problem is type 2 diabetes (Feero et al., 2010), which is preceded by a set of risk factors which comprise the metabolic syndrome (Simmons et al., 2010). Dogs can develop some components of the metabolic syndrome, including insulin resistance (Verkest et al., 2011b) and hyperlipidaemia (Jeusette et al., 2005). Some authors have recently applied the term 'metabolic syndrome' to dogs with naturally-occurring (Tvarijonaviciute et al., 2012) or induced (Kim et al., 2003) obesity. This review examines the evidence for the existence of metabolic syndrome in dogs.

The metabolic syndrome in humans

Type 2 diabetes accounts for over 80% of human diabetes and the prevalence of type 2 diabetes has increased with the prevalence of obesity (Zimmet, 2003). Research into the development of type 2 diabetes has identified obesity, insulin resistance, hyperlipidaemia, and hypertension (among others) as important risk factors for type 2 diabetes, as well as for coronary heart disease and stroke. The term 'metabolic syndrome' describes a clustering of obesity (especially visceral obesity), hypertension, insulin resistance or hyperglycaemia, and hyperlipidaemia (Alberti et al., 2006, 2009).

The metabolic syndrome as a set of risk factors

The metabolic syndrome was developed as a pathophysiological entity in humans after it was highlighted by Reaven (1988), who argued that insulin resistance was the pathophysiological driver of the metabolic syndrome, type 2 diabetes and cardiovascular disease (Reaven, 2011). Various definitions of the metabolic syndrome have been devised and reflect the same pathophysiological mechanism, namely, that obesity, especially visceral obesity, contributes to high blood pressure, resistance to the glucose-lowering effects of insulin, increased circulating triglycerides and decreased HDL (high-density lipoprotein) cholesterol (Alberti et al., 2006, 2009). A recent consensus statement harmonised the definition of the metabolic syndrome as the presence of 3/5 components: plasma triglyceride >150 mg/dL (>1.7 mmol/L); HDL cholesterol <40 mg/dL (<1.03 mmol/L) in men or 50 mg/dL (<1.29 mmol/L) in women; blood pressure >135/85 mmHg; plasma glucose >100 mg/dL (5.6 mmol/L), and gender- and ethnicity-adjusted excessive waist circumference (Alberti et al., 2006, 2009).

The metabolic syndrome itself causes no clinical signs (Simmons et al., 2010). Rather, it comprises a set of important risk factors for diseases that cause morbidity and mortality in humans, including atherosclerosis, coronary heart disease, stroke, and type 2 diabetes (Simmons et al., 2010; Fig. 1a). Atherosclerosis is critical to the pathophysiology of coronary heart disease and stroke. Type

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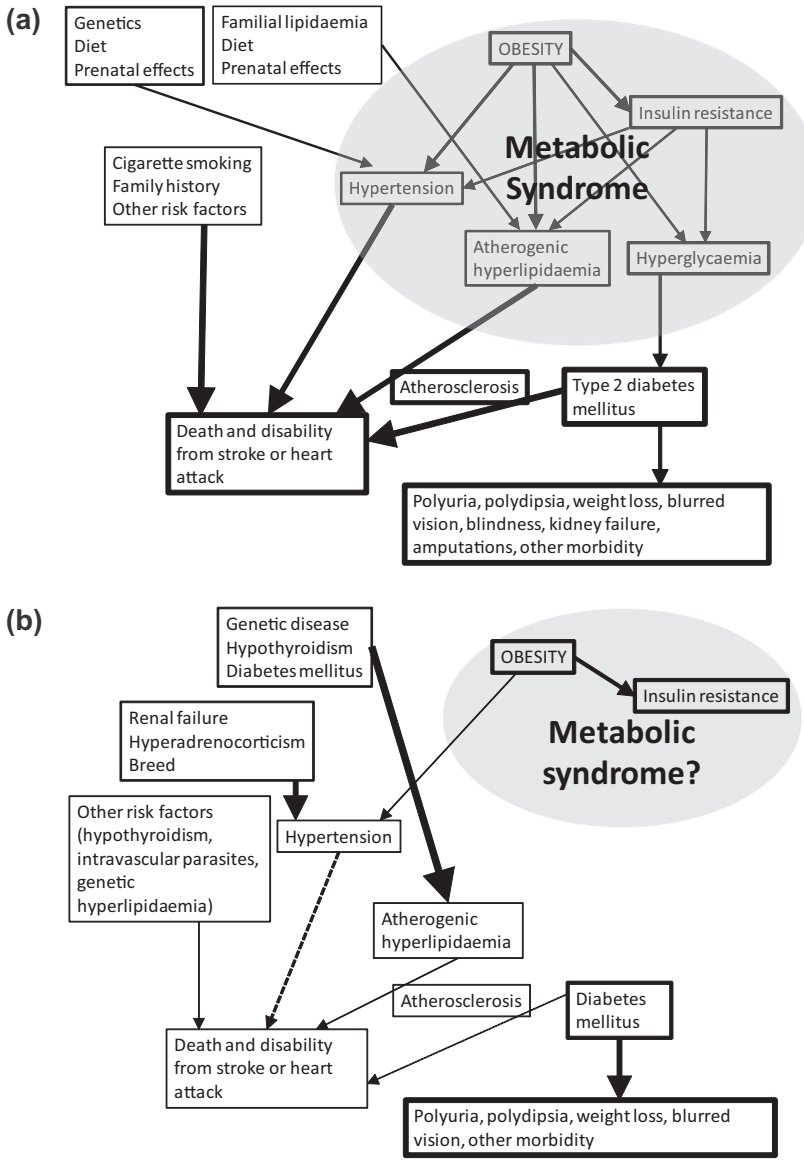

Fig. 1. (a) Simplified flow chart of the components of the metabolic syndrome and their relationship with heart attack and stroke, the leading causes of morbidity and mortality in humans. Obesity promotes hypertension, atherogenic hypercholesterolaemia and hypertriglyceridaemia, and fasting and postprandial hyperglycaemia. These in turn contribute to the formation of atherosclerosis which is a key component of the pathogenesis of heart attack and stroke. The metabolic syndrome in humans links a cluster of risk factors by a common aetiology and leads to clinically important diseases. (b) In dogs, heart attack and stroke are rare and appear to be associated with conditions that are not obesity-induced. Atherosclerosis is a rare complication of endocrinopathies that are not obesity-induced. Hyperlipidaemia associated with obesity does not have the characteristics of atherogenic hyperlipidaemia in dogs. The effect of obesity on hypertension is equivocal and hyperglycaemia appears not to occur as a result of obesity in dogs. The components of the metabolic syndrome are not united by a shared aetiology nor linked to clinically important disease entities.
Thick arrows indicate strong effects, thin arrows indicate minor or rare effects, dashed arrows indicate effects that are not currently proven or are of uncertain importance. Thick box outlines indicate common conditions in each species, thin box outlines indicate rare conditions.

2 diabetes and the metabolic syndrome promote atherosclerosis by causing atherogenic dyslipidaemia, which primarily involves altered cholesterol concentrations. Cholesterol circulates in lipoprotein complexes, including very low density and low density lipoprotein (VLDL and LDL) and HDL. LDL contributes to atherosclerosis whereas HDL protects against atherosclerosis (Anon, 2002; Bauer, 2004).

The lipid component of the human metabolic syndrome is defined as increased fasting triglycerides and decreased HDL cholesterol (Alberti et al., 2006, 2009). Triglycerides are not themselves atherogenic but are markers of atherogenic cholesterol-rich lipoprotein remnants (Anon, 2002). Coronary heart disease causes death and heart failure, whereas stroke causes death and permanent neurological deficits. Type 2 diabetes can lead to blindness, kidney failure and lower limb amputations and further increases the risk of coronary heart disease and stroke (Simmons et al., 2010),

Type 2 diabetes is associated with visceral obesity and insulin resistance (Brouwers et al., 2012) and is regarded as a disease that requires two concurrent metabolic problems. The first is insulin resistance (caused by genetics, obesity, drugs, or other causes). The second is failure of compensatory insulin secretion (Carr and Brunzell, 2004). Both are required before glucose homeostasis is dysregulated. As long as insulin resistance is compensated for by adequate insulin secretion, fasting and postprandial glucose concentrations remain normal (LeRoith, 2002).

Early-stage failure of compensatory insulin secretion results in either mildly elevated fasting or post-prandial glucose concentra-