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DEXAMETHASONE-INDUCED METABOLIC SYNDROME: RE-EVALUATION OF AN UNDERESTIMATED EXPERIMENTAL MODEL

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Dexamethasone is a fluorinated steroid and a synthetic member of glucocorticoids. It is an approved medication for inflammatory and allergic disorders. Also, it is clinically used in high doses to manage pain associated with metastatic osteolytic lesions. Furthermore, it has a wide array of side effects, particularly at high doses and after prolonged consumption, like; hypertension, hyperglycemia, and dyslipidemia. It is a promising tool for studying the underlying mechanisms of metabolic syndrome and insulin resistance. This review article discusses metabolic syndrome and insulin signaling. In addition, this review article will discuss metabolic-dexamethasone effects on the skeletal muscle, liver, adipose tissue, pancreas, brain, and the cardiovascular system, its underlying mechanisms of action, and the benefits of use, in comparison to the other dietary and chemical models of insulin resistance and type 2 diabetes, to identify new potential pharmacological treatments of the metabolic syndrome and its related complications.

Keywords: *Dexamethasone · Diabetes · Metabolic syndrome · Animal model.*

INTRODUCTION

In 1948, it was the beginning of the use of cortisone. The therapist used it to treat a desperately ill long-bedridden 29-year-old woman with severe rheumatoid arthritis. Three days after injections, she miraculously recovered and even went shopping. That single event initiated the cortisone era[1]. Due to salt and water retention of cortisone, several attempts tried to synthesize derivatives with higher glucocorticoid- and lower mineralocorticoid effects, which led to the discovery of dexamethasone in 1958 by a group of chemists at Merk Corporation. Dexamethasone is a fluorinated steroid and a synthetic member of glucocorticoids, which has anti-inflammatory activity 25-times higher than hydrocortisone and long action duration[2] – (figure1)

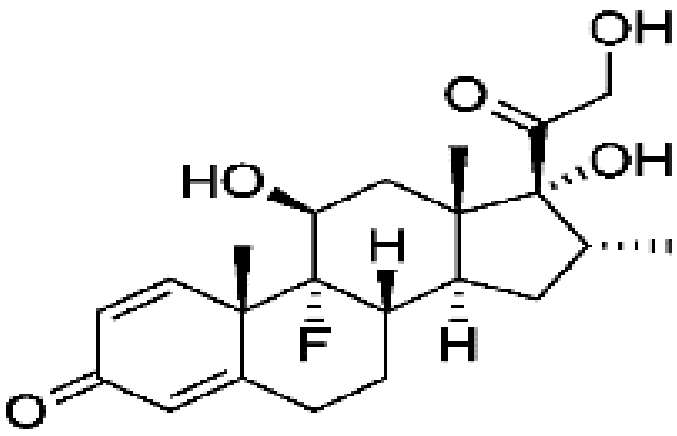

Fig. 1: Dexamethasone; 1-dehydro-9α-fluoro-16α-methyl-hydrocortisone[156].

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Dexamethasone has a long history of clinical uses in treating inflammatory and autoimmune disorders, cancer, and their related nausea and vomiting[3]. In addition, reducing aortic plaque formation is accomplished by dexamethasone uses[4], postoperative facial edema[5&6], and in the treatment of asthma and chronic obstructive pulmonary disease[7&8]. Moreover, dexamethasone has been present to ameliorate the severe respiratory complications associated with COVID-19 infection[9].

Despite these benefits, long-term use of dexamethasone-high-doses leads to serious systemic and metabolic side effects such as hypertension[10], hyperglycemia[11], dyslipidemia[4&12&13], osteoporosis[14&15], and immunosuppression[16]. These side effects are highly correlated with the glucocorticoid activity of dexamethasone[17] and led to using dexamethasone as an experimental model of insulin resistance[18&19] and metabolic syndrome[17].

Metabolic syndrome

Metabolic syndrome is a collection of disorders related to metabolic disturbances such as insulin resistance, hyperglycemia, dyslipidemia, and hypertension[20&21]. This syndrome is also known as dysmetabolic, insulin resistance, and X-syndrome[22]. The prevalence of metabolic syndrome rapidly increases worldwide, even in children[23], due to widespread of sedentary lifestyles and consumption of high calories fast foods[24]. Patients with this syndrome usually suffer from an increased risk of stroke, cardiovascular disorders[25], and different types of cancer[26]. Noteworthy, insulin resistance is considered the main component and the cornerstone of this syndrome[27].

Insulin signaling and glucose uptake

Pancreatic β-cells release insulin in response to hyperglycemia in-vitro[28] and in-vivo[29]. Insulin binding to its receptor on the cell membrane initiates a series of intracellular changes secondary to autophosphorylation of the insulin receptor (IR)-tyrosine residues and subsequently conformational changes[30]. Activated IR stimulates the insulin-receptor-substrate-1 (IRS-1) through tyrosine phosphorylation[31]. This phosphorylation forms a docking site to Src homology-2 (SH-2) domain-containing proteins like phosphatidylinositol 3-kinase (PI3K)[32]. Activated PI3K mediates phosphorylation of phosphatidylinositol 4,5-bisphosphate (PIP2) to phosphatidylinositol 3,4,5-trisphosphate (PIP3), which activates protein kinase B (Akt) [33, 34]. Then, Akt induces the translocation of glucose transporters (GLUTs) from their vesicles in the cytoplasm to the cell membrane, facilitating glucose entrance[35] (figure 2).

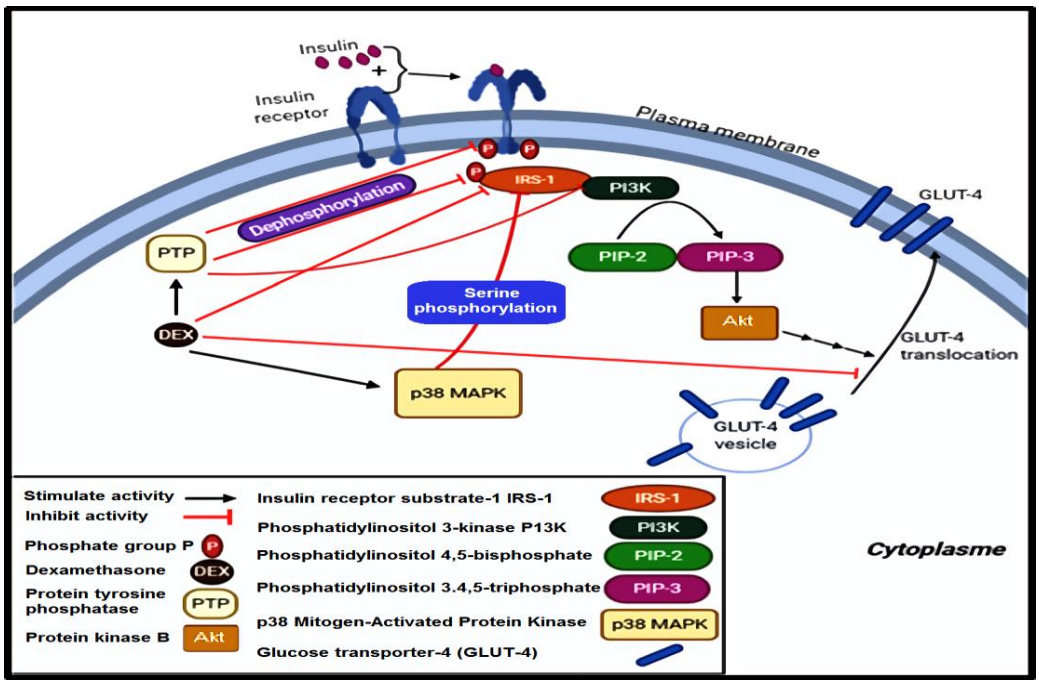

Fig. 2: Insulin signaling pathways and sites of dexamethasone interaction.

Metabolic effects of dexamethasone and glucocorticoids on different body organs

Skeletal muscles

Skeletal and cardiac muscles consume 80% of insulin-induced glucose uptake in the human body[36]. In skeletal muscles, glucocorticoids induce insulin resistance by reducing the transcription of IRS-1 and the extracellular signal-related kinase-3[37&38] while increasing the transcription of proteins that obstruct insulin action like; protein tyrosine phosphatase type-1B (PTP1B) and p38 mitogen-activated protein kinase (p38 MAPK) [39]. In the same context, treating mice with dexamethasone causes significant reductions in Akt activity[40]. Dexamethasone also decreases glucose transporter-4 (GLUT4) translocation, an effect mediated by inhibition of adenosine monophosphate-activated protein kinase (AMPK)-Rab-GTPase–activating proteins (TBC1D1) phosphorylation[40]

TBC1D1 is a Rab GTPase-activating protein, expressed abundantly in skeletal muscles[41], and can be phosphorylated at Ser 237 by AMPK[42]. An activated state of Rab-GTP promotes translocation of GLUT4 to the cell membrane, thus enhancing the capture of glucose in skeletal muscles[43-45] (figure 3).

Liver

In the liver, dexamethasone down-regulates the gluconeogenic enzymes like glucose-6-phosphatase catalytic subunit (G6PC), pyruvate carboxylase (PC), and cytosolic form of phosphoenolpyruvate carboxykinase1 (PCK1). However, it enhances the mitochondrial subtype (PCK2)[46]. On the contrary, the levels of IRS-1 and PI3K oddly increase while their phosphorylation and activities sharply decrease[47].

In the same context, dexamethasone elevates the hepatic levels of triglycerides and induces hepatic steatosis even after a relatively short time interval of treatment[48&49]. In human hepatoma cell lines (Huh7), dexamethasone inhibits the leptin-induced Janus kinase/signal transducers and activators of the transcription (JAK2/STAT3) pathway through the activation of MAPK cascades[50]. This inhibitory action impairs the regulatory effect of leptin on food intake and energy expenditure.

Moreover, Feng and his collaborators showed that dexamethasone-induced hepatic steatosis through upregulation of the mitogen-activated protein kinase phosphatase-3 (MKP-3). This induction of MKP-3 expression is dependent on forkhead box protein- O1, (FOXO1)[51], (figure 3).

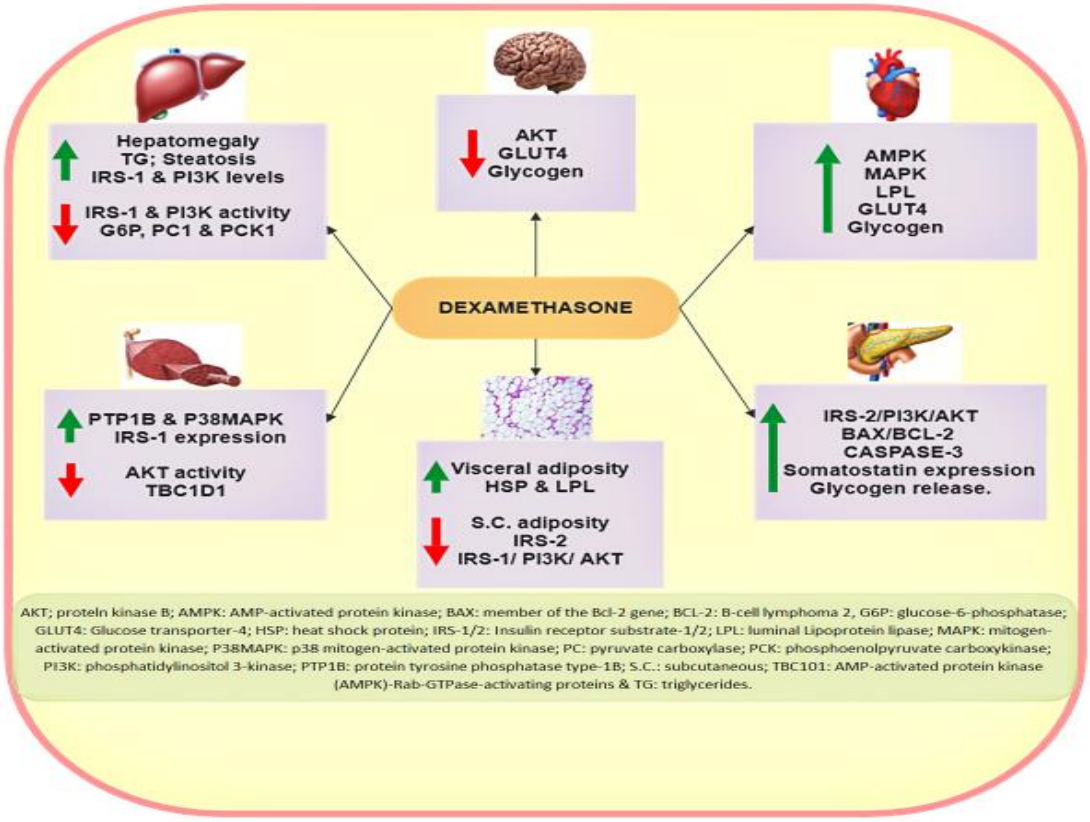

Fig. 3: Summary of dexamethasone-metabolic effects on different body organs.

Adipose tissue

Glucocorticoids are highly active in adipose tissue due to the high expression level of glucocorticoid receptors. Glucocorticoids enhance visceral adiposity while inducing loss of subcutaneous fatty deposits in the arms and legs[52].

Dexamethasone induces lipolysis of subcutaneous fat by increasing the expression of the hormone-sensitive lipase and mediates the hydrolysis of the triacylglycerol of the lipid droplet of adipocytes into glycerol and non-esterified fatty acids[53]. In addition, dexamethasone induces visceral adiposity via activating lipoprotein lipase[54].

Incubation of adipose tissue of rat epididymis with dexamethasone for 24 hrs causes a marked decline in the IRS-1, a slight decrease in PI3K, and a significant reduction in phosphorylated Akt content, whereas IRS-2 content increases[55]. Furthermore, this 24-hrs incubation with dexamethasone significantly reduces the cell-surface insulin binding while increasing the lipolysis and glycerol release[53,56]. In contrast, the short incubation (two to eight hrs) with dexamethasone does not show changes in the IRS-1, PI3K, or phosphorylated Akt content[55]. In the same context, dexamethasone enhances the accumulation of fat deposits in skeletal muscles provoking insulin resistance[57-59] (figure 3).

Pancreas

Treatment of rats with dexamethasone (0.5-1 mg/kg) activates and raises the IRS-2/PI3K/Akt/p70S6K pathway in the pancreatic β-cells leading to increased cellular proliferation[60&61]. However, dexamethasone, in a dose of (0.1 μM for 72 hrs) boosts p53 protein expression in rat pancreatic cells (insulinoma INS-1 cells). This induction increases Bax but decreases B-cell lymphoma 2 (Bcl2) protein expressions and liberates cytochrome c from the mitochondrial membrane[62], leading to enhancement of caspase-3 activity and apoptosis[63].

Notably, rats treated with dexamethasone had shown an increase in pancreatic somatostatin gene expression and protein content[64]. Although Somatostatin inhibits the pancreatic α- and β-cell functions, dexamethasone administration results in hyperglucagonemia and hyperinsulinemia (figure 3).

Heart and blood vessels

Unlike skeletal muscles, cardiac muscles require prolonged exposure to dexamethasone to become insulin resistant[65&66].

Treatment of cardiomyocytes with dexamethasone for two hrs activates stress kinases such as AMPK and MAPK, which phosphorylates the heat shock protein (HSP)25 and causes rearrangement of actin cytoskeleton[65]. In addition, dexamethasone increases the luminal lipoprotein lipase (LPL) activity leading to a breakdown of triglycerides and librates of free fatty acids, which impair cardiac functions[65].

Moreover, dexamethasone can impair cardiac functions and induce left ventricular hypertrophy by elevating the cardiac glycogen content[67]. Dexamethasone elevated cardiac glycogen levels by decreasing glycolysis and increasing glucose uptake by GLUT4 and glycogen synthesis[66]. GLUT4 activity increases secondary to activation of AMPK by dexamethasone[66,68].

On the other hand, dexamethasone induces dose-dependent changes in the aorta. A mild to severe thickening of tunica intima and tunica media was produced by (1-16 mg/kg) dexamethasone doses, leading to the development of severe arteriosclerosis[48] (figure 3)

Brain

Like other organs, the brain also is insulin-sensitive[69]. Most brain cells express insulin receptors but with different densities[70&71]. The brain consumes 20% of blood glucose, despite its weight and size (2% of total body weight)[72].

Treatment of rats with corticosteroids does not affect the expression level of insulin receptors but decreases its activity leading to decreased Akt activity and GLUT4 translocation[73]. These changes are associated with plasticity decline and dysfunction of the neuronal hippocampal cells[73&74].

Dexamethasone reduces glycogen content and modulates the gene expression of neuropeptides and neurotransmitters in the hypothalamus leading to disturbance of animal eating behavior[75] (figure 3).

Other metabolic effects of dexamethasone and glucocorticoids

Hypertension is a common side effect of

dexamethasone[10]. However, the precise mechanism of dexamethasone-induced hypertension is unclear[76&77], but it is most likely to be mediated by peripheral rather than central effects because dexamethasone does not readily pass the blood-brain barrier[78].

Dexamethasone can induce hypertension via mineralocorticoid receptor activation, leading to renal sodium and water retention[78&80]. In addition, dexamethasone can enhance angiotensin II production by increasing angiotensin II converting enzyme activity[81] and can up-regulate the expression of the angiotensin II type 1 receptor in the vascular smooth muscle cells[82]. Furthermore, dexamethasone increases catecholamine biosynthesis in the adrenal medulla and enhances smooth muscle contractility response to adrenergic agonists[83&84].

In the same context, dexamethasone can quench the nitric oxide content of endothelial cells of the blood vessels through the production of reactive oxygen species such as superoxide[85&86]. Therefore, using anti-oxidants can reverse dexamethasone-induced hypertension[87].

Dose- and time-dependent metabolic effects of dexamethasone

Low-dose-dexamethasone (0.005 mg/kg/day) significantly induced insulin resistance after seven days of treatment, hypertension after 15 days, and dyslipidemia after 28 days in Wistar rats[88]. Changes in the body, liver, heart and kidney weight even after 28 days had not been seen. Also, blood glucose levels remained normal during the same period of treatment. Insulin resistance may attribute to dexamethasone-induced endothelial dysfunction[88].

Dexamethasone (0.13 mg/kg/day) provoked insulin resistance, hyperinsulinemia, and elevated plasma-free fatty acids from 4 -13 days. Blood glucose levels stayed normal over the 13-days-period of study. Food intake and weight of the body and pancreas significantly decreased after 13 days of treatment[89].

Dexamethasone (1 mg/kg/day) had impaired glucose tolerance and liver functions and induced dyslipidemia after eight days of treatment in rats. Body weights decreased while liver weights increased compared to the control group. Blood glucose levels and weight of the heart, pancreas, and kidney remained normal[90].

Dexamethasone (10 mg/kg/day) has induced hyperinsulinemia, dyslipidemia, hepatomegaly, liver steatosis, cardiac injury, and proteinuria after seven days of treatment. Body weights decreased while blood glucose levels remained normal. The mortality rate in this model was 22 % when dexamethasone was injected by the subcutaneous route, whereas the intraperitoneal route induced death in 80% of animals (data under publication) (Table 1).

Dexamethasone vs. dietary models of insulin resistance and metabolic syndrome

Dietary models of insulin resistance include the use of high-fructose, high-sucrose, high-fat, and high-fructose-high-fat diets.

Fructose is a monosaccharide that mediates the accumulation of triglycerides and cholesterol if consumed in high amounts[91&92]. High-fructose-diet regimens usually contain 10 to 60% fructose of the total content[93-95]. These regimens can prompt metabolic syndrome within 3-16 weeks[93-97]. This model produced overt high visceral adiposity, hypertriglyceridemia, hyperlipidemia, hypertension, glucose intolerance, insulin resistance, hyperuricemia, oxidative stress, and inflammatory markers[93-96,98&99].

Sucrose is a disaccharide of fructose and glucose[100]. Fructose is the main component of sucrose-rich diets that mediates metabolic syndrome[99] because fructose is better than glucose as a substrate for hepatic fatty acid synthesis[101]. Administration of 30 to 77% sucrose in the diet can induce metabolic syndrome in experimental animals within 10 to 21 weeks, characterized by hyperglycemia, dyslipidemia, hypertension, and hyperinsulinemia[97&102&103].

A high-fat diet is the most widely used regimen to induce metabolic syndrome. Fats, either plant- or animal-derived, in concentrations of 20 to 60% of the diet can encourage visceral adiposity, insulin resistance, mild hyperglycemia, and dyslipidemia within 8 to 16 weeks[97&104]. Also, high-carbohydrate-high-fat diets are now widely used in the induction of metabolic syndrome within 4- 42 weeks, discriminated by hypertension, glucose intolerance, visceral adiposity, and dyslipidemia[105-107]. This model may be faster than the other traditional dietary models[108].

The lower cost of dexamethasone[97] and the short time of metabolic syndrome induction[108-111] made it the most affordable and time-saving model. However, the main drawback of this

model is that it does not mimic the reality like; weight gain[89,90,112]. Also, inflammation has no role in this model[113], in contrast to dietary ones[95,98,114]. Consequently, the anti-inflammatory-therapeutic effects of some drugs like; insulin sensitizer cannot detect via it (Table 2).

Table 1: Dose- and time-dependent metabolic effects of dexamethasone in experimental animals**.**

Dose	Route	Duration (Days)	Metabolic Effects	Species	Reference
0.001-0.01 mg/kg	IV	28	Hypertension; weight gain	Sprague-Dawley rats	[133]
0.005 mg/kg	SC	28	Dyslipidemia; hyperinsulinemia	Wistar rats	[88]
0.01 mg/kg	Orally	14	Weight loss	Wistar rats	[134]
0.07-0.44 mg/kg	IV	28	Hyperglycemia; weight loss	Wistar rats	[135]
0.1-0.5 mg/kg	IP	5	Weight loss	Wistar rats	[110]
0.2 mg/kg	IP	21	Hyperglycemia; hyperinsulinemia; weight loss	Sprague-Dawley rats	[136]
0.5 mg/kg	IP	15	Hyperglycemia; dyslipidemia; weight loss	Wistar rats	[111]
1 mg/kg	IP	10	Hyperglycemia; hyperinsulinemia; dyslipidemia; weight loss	Wistar rats	[19]
1 mg/kg	IP	5	Hyperglycemia; dyslipidemia; hyperinsulinemia; weight loss	Wistar rats	[110]
1 mg/kg	IM	22	Hyperglycemia; hypertriglyceridemia; hyperinsulinemia; weight loss	Swiss albino mice	[137]
1 mg/kg	Parenteral	5	Hyperglycemia	Male rats	[47]
1 mg/kg	IP	10	Hyperglycemia; hyperinsulinemia; weight loss	Wistar rats	[19]
2.5 mg/kg	IP	42	Dyslipidemia; liver steatosis; weight loss	C57BL/6J mice	[138]
4 mg/kg	SC	3	Hyperglycemia	Wistar rats	[139]
10 mg/kg	SC	10	Hyperglycemia	Wister albino rats	[140]
10 mg/kg	SC	8	Hyperglycemia; hyperinsulinemia; dyslipidemia; weight loss	Male albino rats	[112]
120 µl 0.1%	Ocular	30	dyslipidemia	C57BL/6J mice	[141]
150 µl 0.1%	Ocular	30	dyslipidemia; weight loss	Sprague-Dawley rats	[142]

IM: intramuscular, IP: intraperitoneal, IV: intravenous & SC: subcutaneous.

Table 2: Time-dependent metabolic effects of dietary models of insulin resistance**.**

Diet regimen	Duration (Weeks)	Metabolic Effects	Species	Reference
HFrD (60%)	3	Hyperglycemia; hyperinsulinemia; hypertension.	Wistar rats	[143]
	7	Hypertension; hyperinsulinemia; dyslipidemia	Sprague-Dawley rats	[144]
	8	Hypertension; hypertriglyceridemia; hyperuricemia; kidney hypertrophy.	Sprague-Dawley rats	[93]
	16	Hyperglycemia; hyperinsulinemia; hyperlipidemia; hyperuricemia.	Wister albino rats	[96]
Fr. in drinking water (10%)	8	Hyperinsulinemia; dyslipidemia.	Wistar rats	[94]
	12	Hyperglycemia; hypertension; hyperinsulinemia; dyslipidemia; hyperuricemia.	Wistar rats	[95]
Su. in drinking water (12 %)	7	Hypertension; mild hyperinsulinemia	SH rats	[144]
Su. in drinking water (32 %)	10	Hyperglycemia; hyperinsulinemia; dyslipidemia	Sprague-Dawley rats	[102]
Su. in drinking water (30 %)	21	Hypertension; hyperinsulinemia; dyslipidemia	Wister albino rats	[145]
HFD (32%)	10	Hyperglycemia; dyslipidemia.	Sprague-Dawley rats	[146]
HFD (62%)	12	Hyperinsulinemia; dyslipidemia	C57BL/6J mice	[147]
HFD (60%)	20	Hyperglycemia; hyperinsulinemia; hypercholesterolemia.	C57BL/6J mice	[148]
HFD (45%)	24	Hyperglycemia; hyperinsulinemia; dyslipidemia.	Sprague-Dawley rats	[104]
HFD (10%)	24	Hyperinsulinemia; dyslipidemia.	C57BL/6J mice	[149]
HFD + STZ (30-40 mg/kg)	10	Hyperglycemia; hypertension; hyperinsulinemia; dyslipidemia	Wistar rats	[150]
HFrHFD	8	Hyperinsulinemia; dyslipidemia.	Wistar rats	[151]
	16	Hyperglycemia; hypertension; hyperinsulinemia; visceral adiposity	Wistar rats	[152]
HFD (45%) + Fr/DW (30%)	4-16	Dyslipidemia (4 m); hyperglycemia; visceral adiposity (8 m); high LDL (16 m)	C57BL/6J mice	[153]
HFD (21%) + HSD (34%)	4	Dyslipidemia; hyperinsulinemia	C57BL/6J mice	[154]
HFD (25%) + HSD (65%)	12	Hyperglycemia; hyperinsulinemia; dyslipidemia.	Sprague-Dawley rats	[155]
HFD (20%) + Fr/DW (10%)	8	Dyslipidemia.	Wistar rats	[151]

Fr: fructose: Fr/DW: fructose in drinking water, HFD: high fat diet, HFrD: high fructose diet, HFrHFD: high fructose, high fat diet, HSD: high sucrose diet, LDL: low density lipoprotein, m: month, Su: sucrose, SH: spontaneous hypertensive, STZ: streptozotocin.

Dexamethasone vs. chemical models of type 2 diabetes

Streptozotocin (40 mg/kg) and alloxan (84 mg/kg) can induce type 2 diabetes within a few days by causing mild damage to the pancreatic β-cells[115&116]. Also, streptozotocin in a higher dose (65 mg/kg) is used in combination with nicotinamide to induce type 2 diabetes[117]. Nicotinamide reduces the cytotoxic effect of streptozotocin[118&119]. Notably, several drawbacks of these chemicals include the high cost, the high mortality rate[120-122], and the absence of insulin resistance[123&124]. To overcome these disadvantages, some models use streptozotocin plus a high-fat diet to induce insulin resistance and type 2 diabetes[125]. However, the latter intervention increases the cost and the time of the experiments. Thus, the dexamethasone model is considered the best cost- and time-saving for studying insulin resistance and metabolic syndrome (Table 3).

Combining dexamethasone with either streptozotocin or dietary models of insulin resistance

Dexamethasone has been used with streptozotocin in a rat model of type 2 diabetes to mimic the β-cell dysfunction and insulin resistance that characterize this model[126&127]. In addition, dexamethasone has been used with a high-fat diet model of insulin resistance in mice to accelerate the progression of insulin resistance within a shorter time compared to a high-fat diet alone[109]. Notably, prenatal administration of dexamethasone followed by postnatal feeding with a high-fat diet in rats causes dysregulation of nutrient-sensing molecules such as circadian-clock genes in visceral adipose tissue[128], as well as the elevation of systolic and diastolic blood pressure and activation of the renin-angiotensin system[129&130]. In the same context, the combination between dexamethasone and sucrose induced a higher level of hyperinsulinemia, hyperglycemia, and hypertriglyceridemia[131&132].

Conclusion

Dexamethasone in a wide range of doses (0.005 up to 10 mg/kg/day) can induce insulin resistance, hypertension, and dyslipidemia within 7 to 28 days compared to a range of 21 to 147 days of corresponding dietary models. The cost of dexamethasone is much lower than dietary and chemical models of type 2 diabetes**.** Dexamethasone induces insulin resistance by modifying the same pathways affected by dietary models except for the inflammatory pathways. The main drawback of the dexamethasone-induced metabolic syndrome model is the absence of weight gain, the main feature of this syndrome in humans. However, dexamethasone remains the best choice regarding the cost and time for experimental investigation of new insulin sensitizers.

Declaration of interests

All authors declare that they have no conflicts of interest, No known competing financial interests, or personal relationships that could have appeared to influence the work reported in this paper.

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متلازمة الأيض المستحثة بالديكساميثازون: إعادة تقييم نموذج تجريبي مقلل من شأنه

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يعد الديكساميثازون من الاستيرويدات اللتي تحتوي على الفلورين وهو مركب مصنع معمليا من مركبات الجلوكوكورتيكويد. كما انه دواء معتمد لأمراض الالتهاب والحساسية. أيضا يستخدم الديكساميثازون اكلينيكا في جرعات عالية للتحكم في الألم المصاحب لاصابة العظم التحللية المرتبطة بالسرطان. على الرغم من ذلك فان لهذا الدواء مجال واسع من الاعراض الجانبية خاصة في الجرعات العالية و بعد استخدامه لفترات طويلة مثل ارتفاع ضغط الدم ومستوى السكر بالدم واضطراب مستويات الدهون بالدم مما يجعله وسيلة واعده لدراسة الأليات المسببه لمتلازمة الأيض ومقاومة الانسولين. يناقش هذا المقال المرجعى متلازمة الأيض واشارات الأنسولين. أضف الى ذلك يناقش هذا المقال المرجعي التأثيرات الأيضية للديكساميثازون على العضلات الهيكلية، الكبد، النسيج الدهني، البنكرياس، المخ و جهاز القلب و الأوعية الدموية و آليات تأثيره وكيفية الاستفاده منه بالمقارنة بالأنظمة الغذائية والكيميائية المسببة لمقاومة الأنسولين والسكري النوع الثاني في تحديد علاجات دوائية جديده وفعاله لمتلازمة الأيض والمضاعفات المرتبطة بها.