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ORIGINAL ARTICLE

Effect of obesity on response to cardiovascular drugs in pediatric patients with renal disease

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Abstract Obesity is associated with an increased concentration of inflammatory mediators, which in turn, in adults, reduces the response to calcium channel blockers (CCBs). We reviewed the medical charts of 263 pediatric nephrology patients with renal conditions, with the aim of studying the effect of obesity on the response to L-type CCBs, angiotensin interrupting agents (ANGIs), or a combination of the two. Forty-eight patients were ultimately enrolled in the study: 25 obese and 23 non-obese patients. The effect of the treatments on lowering the blood pressure was compared in obese versus non-obese patients. The systolic response to CCBs, measured as at least a 10% reduction from the baseline, was significantly lower in the obese (12.5%) patients than in the non-obese (52.9%) ones. The differences in diastolic response (58.8 and 25% for non-obese and obese patients, respectively) did not reach significance. The percentage response to CCBs, however, was significantly less in the obese patients than in the non-obese patients for both systolic and diastolic blood pressure. Corticosteroids also significantly influenced the response to CCBs in terms of diastolic pressure (62.9 and 25% for non-obese and obese patients, respectively). None of the tested covariates, including obesity, was found to significantly influence the response to ANGIs alone or in various combinations with CCBs. In conclusion, obesity and corticosteroid therapy should be considered when initiating antihypertensive drug treatment in children with kidney disease as both may contribute to a reduced efficacy of the antihypertensive therapy.

Keywords Angiotension · Calcium channel blockers · Hypertension · Pharmacotherapy · Obesity · Renal disease/dysfunction

Abbreviations

ANGI	angiotensin interupting agents
BMI	body mass index
CCBs	calcium channel blockers
CRP	C-reactive protein
TNF-α	tumor necrosis factor-α

Introduction

The incidence of childhood obesity in North America has increased dramatically over the past three decades [1–4]. Obesity is linked to poor disease outcome in renal transplant patients [5] and increased propensity to some adult conditions, such as cardiovascular diseases [6]. Obesity has also been regarded as an inflammatory process [7, 8] complicated with chronic low-grade inflammation [8, 9]. Overweight and obese children have elevated levels of inflammatory mediators, such C-reactive protein (CRP) and tumor necrosis factor α (TNF-α) compared to the general pediatric population [10–12]. Adult obesity and other inflammatory conditions associated with elevated concentrations of pro-inflammatory mediators, such as rheumatoid arthritis, have been found to be linked to a reduced response to calcium channel blockers (CCBs), such as verapamil [13–16]. This association has been attributed to

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an inflammation-induced reduction in binding to L-type calcium channels [13, 14] and a downregulation of calcium channel target protein [13]. This specific effect of inflammation is important because obesity and other inflammatory states are complications of many diseases, such as hypertension, angina and acute myocardial infarction, which may ultimately require CCB therapy [17–19]. As such, obesity may contribute to poor disease outcome [20].

Pediatric patients with renal disease have an increased propensity to hypertension compared to children with normal renal function [19]. This increased propensity has been attributed to many factors, such as activation of the renin–angiotensin–aldosterone system, fluid overload, and corticosteroid therapy [19]. Calcium channel blockers, such as nifedipine and amlodipine, and angiotensin converting enzyme inhibitors, such as ramipril and enalapril, are the most commonly prescribed drugs to treat hypertension in children with renal disease [21–23]. However, the effect of obesity on the pharmacological response of these drugs in children with renal disease has not yet been studied.

The aim of this study was to investigate the effect of obesity on the pharmacodynamic response to CCBs or angiotension II blockers in pediatric patients with renal disease who are currently prescribed these classes of drugs.

Patients and methods

A retrospective chart review study was conducted on the health records of 263 pediatric patients treated for renal disease at the Pediatric Nephrology Outpatient Clinic at the University of Alberta Hospital/Stollery Children's Hospital between 2002 and 2006. The study was approved by The Health Research Ethics Board at University of Alberta. Patient medical records were chosen based on the International Classification of Diseases, 9th edition (ICD-9 [24]) codes for renal conditions in which antihypertensive therapy are routinely employed (Table 1). Patients were allocated to a diagnosis category based on the identification of coding priority. Figure 1 shows the study design. Charts were reviewed to identify whether antihypertensive medications were prescribed to these patients. Inclusion criteria were male or female gender; age < 18 years; treatment with CCBs (nifedipine or amlodipine) or angiotensin interrupting agents [ANGI; includes angiotensin converting enzyme inhibitors (i.e. captopril, ramipril, enalapril) and angiotensin II receptor blockers (i.e. candesartan, losartan, and valsartan)] either alone or a combination of the two; medical chart with sufficient demographic data and blood pressure measurements.

The data collected were age, sex, weight, height, body mass index (BMI), drug treatment, dosage, and pre- and post-therapy blood pressure measures. Weight, height, and BMI percentiles were determined for each patient using specific nomograms for the corresponding age and sex [25]. Blood pressure had been measured according to the recommendations of the fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents [26]. The measurement had been carried out by physicians and/or nurses using manual/auscultatory methods. All measurements had been made in the hospital, and there had been at least three measurements per patient. The average of the measurements was recorded for the study. Systolic and diastolic blood pressure, 95th percentile values for the corresponding age, sex, and height of the patient were also determined for each patient using 2004 guidelines [26]. Systolic percentiles for patients younger than 1 year of age were determined using the 1987 guidelines [27]. Patients were considered to be hypertensive if their blood pressure values ≥ 95th percentile blood

Table 1 Diagnostic codes of the International Classification of Diseases, used in this study [24]

Coding priority	ICD-9 code	Diagnosis	Number of patients included
1	585	Chronic renal failure	5
	593.X	Chronic renal insufficiency	
2	580.X	Acute glomerulonephritis	8
	583.X	All glomerulonephritis	
	599.7	Hematuria	
	287.0	Henoch Schönlein purpura (glomerulonephritis)	
	582.X	Chronic glomerulonephritis	
3	581.X	Focal segmental glomerulonephritis and nephrotic syndrome	23
4	593.X	Reflux nephropathy	3
	596.X	Bladder dysfunction	
	753.X	Urologic abnormalities	
	589.X	Urologic abnormalities	
5	401.9	Hypertension (without identified cause)	9

ICD-9, International Classification of Diseases, 9th edn

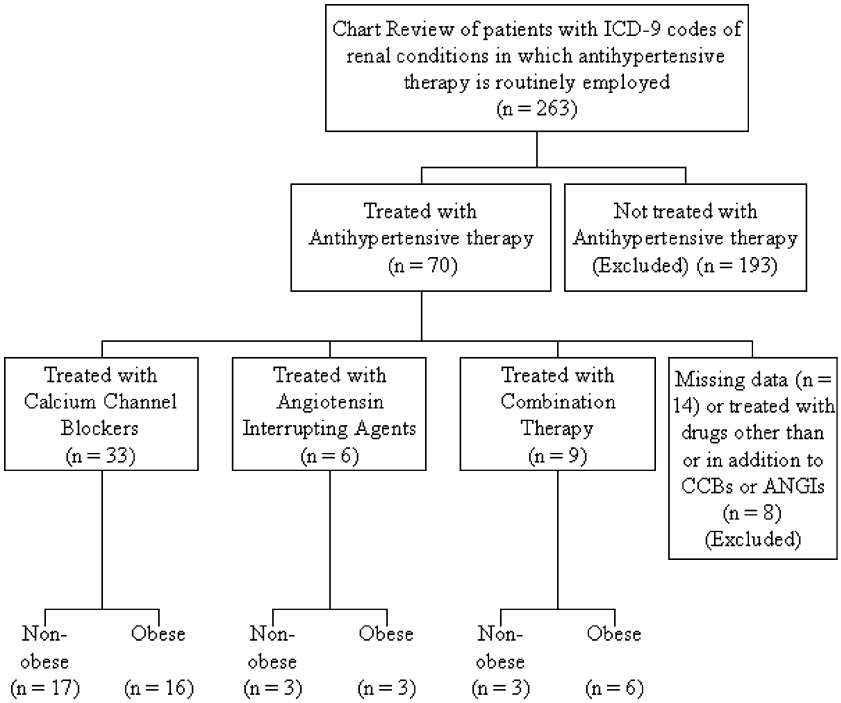

Fig. 1 Flow chart of patients recruitment and grouping strategy. *ICD-9* International Classification of Diseases, 9th edn, *CCB* calcium channel blocker, *ANGI* angiotensin converting enzyme inhibitors and angiotensin II receptor blockers

pressure for the corresponding age, sex, and height [26]. Patients' characteristics depicted in Table 2 were compared between the obese and non-obese patients using the two-tailed Student's *t* test.

An obese patient aged between 2–18 years was defined as an individual with a BMI ≥ 95th percentile for healthy children of the corresponding age and sex [6]. Patients younger than 2 years of age whose weight percentile ≥ 95th percentile of children of the corresponding age and sex were also considered to be obese.

The influence of obesity on the effects of CCBs and ANGIs to lower the systolic and diastolic blood pressure was determined. Two outcome variables were measured. First, patients were categorized as responders or non-responders based on at least a 10% reduction from the baseline systolic and/or diastolic blood pressure. The effect of obesity was tested using multivariate logistic regression [28]. Second, the percentage reduction in the blood pressure from the baseline was measured and compared between obese and non-obese patients using the two-tailed Student's *t* test. The effect of other covariates, i.e. age, sex, diagnosis, and corticosteroid therapy, on drug response was also tested using multivariate logistic regression. The p value was set at < 0.05. Statistical analyses were carried out using Statistical Analysis System (SAS) software ver. 9.1 (SAS Institute, Cary, NC).

Results

The medical records of 263 patients were reviewed. The highest number of patients on antihypertensive therapy

Table 2 Characteristics of the patient cohort

Patient characteristics	Non-obese	Obese
Number (%)	23 (48)	25 (52)
Age, years (range)	8.5±0.7 (2.58–15)	8.3±1.1 (0.17–16)
Sex, number (%)		
Males	12 (52.17)	21 (84)*
Females	11 (47.83)	4 (16)
Height, cm (range)	131±4.2 (92–169.4)	124.4±7.5 (48–180)
Height, percentile	57.6±7.3	54.2±6.9
Weight, kg (range)	32.5±3.0 (12–61.3)	47.1±6.3* (6.6–114.8)
Weight percentile	59.6±6.6	93±1.1*
Body mass index, kg/m^2 (range)	17.9±0.7 (12.4–24.8)	26.5±1.2* (18.6–37.1)
Body mass index, percentile	61.3±6.1	95±0*

*$p<0.05$ from non-obese
Where appropriate, values are given as mean ± standard deviation

Table 3 Mean doses[a] of calcium channel blockers and angiotensin interrupting agents

CCBs/ANGIs	Non-obese	Obese	*p* value
Amlodipine (CCB)			
Number[b]	7	2	0.60
Dose	6.9±1.2	8.3±2.5	
Nifedipine (CCB; short acting)			
Number	11	13	0.73
Dose	10.7±2.4	9.6±1.9	
Nifedipine (CCB; long acting)			
Number	2	7	0.56
Dose	77.2±34	56±15.8	
Ramipril (ANGI)			
Number	4	4	0.36
Dose	7.7±1.0	5.6±1.9	
Other ANGIs (enalapril comparative dose) [26, 43]			
Number	2	5	0.97
Dose	4.9±3.7	5.0±0.9	

CCB Calcium channel blocker; *ANGI* angiotensin interrupting agents
[a] All doses reported in this table are given as mg/m^2 per day (mean ± standard deviation)
[b] Number indicates the number of patients

were those who, according to the ICD-9 diagnostic list, had been placed in the hypertension (100%) category, followed by the nephrotic syndrome (65%) category. The lowest percentage of patients on antihypertensive therapy (5%) were those with urologic abnormalities. Overall, 70 patients were found to be treated with antihypertensive drugs: chronic renal failure (n=6), glomerulonephritis and related conditions (n=11), nephrotic syndrome (n=35), urologic abnormalities (n=6), and hypertension (n=12). The patient distribution based on their glomerular filtration rate (GFR; ml/min per 1.73 m^2) was 7% at ≥ 90, 13% at 60–90, 20% at 30–59, 27% at 15–29, and 33% at <15 ml/min per 1.73 m^2. All patients with nephrotic syndrome were hypoalbuminemic.

Six patients were excluded because they were missing height values needed for determining BMI and blood pressure percentiles. Another eight patients were excluded because they were being treated with antihypertensive medications other than or in addition to CCBs and ANGIs. Of the latter eight excluded patients, five were obese. They had been treated with multiple medications because they were resistant to therapy. Another eight patients were on antihypertensive medications before the assessment by the clinical service and so they were excluded from the study. Consequently, a total of 48 patients were included in the study (Table 2). Age and height distributions were not significantly different between obese and non-obese patients. There were significantly more obese males than females (p<0.05). Twenty-five patients (ten non-obese and 15 obese) were on corticosteroid therapy. Of these, 20 were treated by prednisone before and five after the assessment. The average dose of prednisone was 47±4.0 and 43.7±6.5 mg for non-obese and obese patients, respectively. The average time to the second blood pressure measure was 3.0±0.27 days (range 2–5) for non-obese patients and 3.3±0.22 (range 2–5) days for obese patients.

Thirty-three patients (17 non-obese and 16 obese) were treated with CCBs (amlodipine, nifedipine XL, or regular acting nifedipine), six patients were treated with ANGIs (captopril, ramipril, enalapril and losartan), and nine

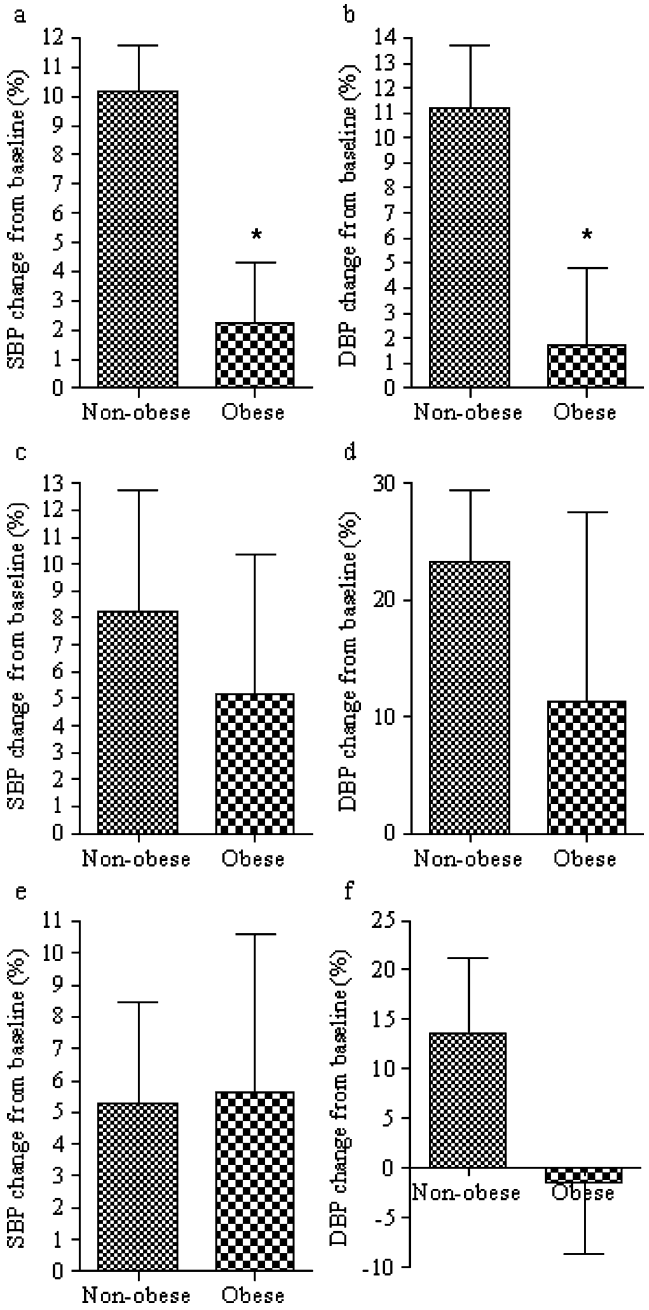

Fig. 2 Percentage changes in systolic (*SBP*) and diastolic (*DBP*) blood pressure from baseline in obese and non-obese patients treated with calcium channel blockers (**a**, **b**), angiotensin interrupting agents (**c**, **d**) or a combination of the two (**e**, **f**). *p<0.05 from non-obese

patients were treated with a combination of an ANGI and a CCB. There was no significant difference in CCB and ANGI dosages between obese and non-obese patients (Table 3).

The systolic response to the calcium channel antagonist therapy, measured as at least a 10% reduction from the baseline, was significantly less in the obese (12.5%) than the non-obese (52.9%) patient group. With respect to the diastolic response, although numerically different between the groups (58.8 and 25% for non-obese and obese patient group, respectively), no significance was reached. For the percentage reduction in systolic and diastolic blood pressure, the influence of the calcium channel antagonists was significantly less in obese than non-obese patients (Fig. 2). Among the examined covariates, only obesity and corticosteroid therapy had a significant influence on the systolic and diastolic response to calcium channel antagonists, respectively (Table 4). Patients treated with corticosteroid therapy had a significantly reduced diastolic response (25%) to CCBs as compared to non-treated ones (69.2%).

None of the tested covariates, including obesity, were found to significantly influence the response to ANGIs. As depicted in Fig. 2, the percentage reduction in systolic and diastolic blood pressure due to the influence of ANGI therapy, either alone or in combination with CCBs, was not significantly different between the obese and non-obese patients (Fig. 2).

Discussion

In adults, rheumatoid arthritis [16], old age [29], and obesity [15] result in a reduced response to the calcium channel antagonist verapamil. All of these conditions are considered to be chronic low-grade inflammatory states and are all associated with an elevated circulating concentration of pro-inflammatory mediators, such as CRP and TNF-α [8, 9]. The accumulation of adipose tissue in obese individuals has been linked to increased macrophage infiltration and chemokine and cytokine production [7]. Obese children also have elevated serum concentrations of CRP [10–12] and TNF-α [12]. Such observations have been made under diverse experimental conditions in terms of the patient population and drugs used. Our aim was to determine whether obese children also exhibit a lower response to calcium channel therapy than their non-obese counterparts. Based on our data, we suggest that systolic blood pressure in obese children is less responsive to CCBs than that of non-obese children (Fig. 2, Table 4). Since our patients were dosed on the basis of their body-surface area (BSA) rather than their body weight and there was no significant difference in dosages, the possibility of underdosing can be ruled out. The exact mechanism behind this observation is unknown. Data from animal studies indicate that the reduced response to CCBs under inflammatory conditions is due to the downregulation of L-type calcium channels secondary to a reduced drug receptor binding [13, 14], which by itself is caused by depressed target protein expression [13].

All of the pediatric patients enrolled in this study had underlying renal complications (Table 1). Explanations which have been put forward for the high incidence of elevated blood pressure in pediatric patients with renal disease include activation of the renin–angiotensin–aldosterone system, fluid overload, and corticosteroid therapy [19]. These patients are usually treated with antihypertensive drugs, such as CCBs and ANGIs. If we consider the fact that 70 of the 263 patients reviewed in this study (27%) needed antihypertensive therapy, and that of these 70, 50% were obese, our observation becomes clinically relevant. Hypertension by itself is an inflammatory condition, and hypertensive obese children have been found to have higher concentrations of inflammatory mediators than non-hypertensive ones [30]. The magnitude of the reduced response observed in our study may, therefore, be due to a combination of obesity and hypertension. Indeed, we observed the downregulating effect of obesity by including only a relatively small population size in the study.

Table 4 Adjusted odds ratios, 95% confidence intervals, and *p* values of different variables tested for their association with systolic and diastolic responses to CCBs

Covariate	Systolic response			Diastolic response		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
Age	0.98	0.79–1.2	0.85	1.05	0.86–1.3	0.66
Sex (female vs. male gender)	0.36	0.04–3.4	0.38	0.88	0.1–7.5	0.9
Obesity (non-obese vs. obese)	12.26	1.2–122	0.03	3.93	0.6–25.9	0.16
Nephrotic syndrome (non-nephrotic vs. nephrotic)	5.66	0.78–41	0.09	0.17	0.01–1.8	0.14
Corticosteroid therapy (not treated vs. treated)	1.83	0.3–11.7	0.53	15.1	1.3–176	0.03

CI Confidence interval

Obesity was not the only confounding variable; corticosteroid therapy was also associated with a reduced diastolic response to CCBs. Prednisone and methylprednisone are commonly prescribed drugs in a therapeutic program aimed controlling the progression of a number of kidney diseases or as immunosuppressants in renal transplant recipients [17, 31]. Corticosteroids are known to antagonize the antihypertensive effects of drugs [19]. This effect has been explained by three mechanisms: the induction of a positive sodium balance with subsequent water retention; enhancement of the sensitivity of tissues to catecholamines, with subsequent vasoconstriction; central nervous system activation [32, 33].

Patients diagnosed with hypertension-related nephrotic syndrome had the highest requirement for antihypertensive medications. This is an expected result because of the nature of the disease and concomitant treatment with corticosteroids [17, 31]. On the other hand, patients with urologic abnormalities had the lowest requirements for antihypertensive treatment. Thus, a knowledge of the underlying kidney disease and its management can facilitate the prediction of the drug response. Nephrotic syndrome patients were more prone to have a reduced efficacy of antihypertensive medications, possibly explained by hypoalbuminemia-induced water retention, obesity, and corticosteroid therapy [17, 19]. In contrast, hypertensive patients with urologic abnormalities are more likely to respond to medications because they do not have similar risk factors for resistance to therapy.

Although sex was not significantly associated with a reduced drug response, there were more obese males than females. This may explain in part an earlier observation that the long-term antihypertensive efficacy of amlodipine in pediatric patients with chronic kidney disease is significantly higher in females than males [22].

A reduced response to drugs, including CCBs, under inflammation-complicated conditions may contribute to a poor disease prognosis and therapy outcome. Other cardiovascular diseases, such as acute myocardial infarction and heart failure, are also associated with elevated pro-inflammatory mediator concentrations [34, 35]. Indeed, morbidity and mortality in these patients are correlated with the magnitude of such elevations [20]. The potential contribution of receptor downregulation in the poor therapy outcome in these patients cannot be ruled out.

Due to the retrospective nature of the study, we did not have access to the plasma concentration of the antihypertensive drugs; consequently, we cannot equivocally rule out a potential contribution of an altered pharmacokinetics. This limitation to our study is important in light of the potential effect of the hypoalbuminemia observed in our patients. Hypoalbuminemia may cause a reduced plasma protein binding of drugs, resulting in a potential increase in drug concentration at the site of action [36, 37]. This reduced protein binding may also give rise to accelerated overall clearance of the drug. These two potential mechanisms often offset each other and render the influence of hypoalbuminemia on the pharmacokinetics negligible [36-38].

It is not well known if our observations can be extrapolated to the action of other cardiovascular drug in humans. β-Adrenergic receptors are also capable of down-regulation in animal models of inflammation [39]. In contrast, our data indicate that obesity had no significant influence on the potency of ANGIs. This latter result is in agreement with data reported for adults: inflammation does not alter the pharmacological response to angiotensin II receptor blockers, such as valsartan [40] and losartan [41]. This effect has been attributed to the suppression of angiotensin, which is a potent pro-inflammatory mediator [42]. In addition, these drugs have been found to improve proteinuria in a number of kidney diseases, such as nephrotic syndrome and acute glomerulonephritis [23], which is an added advantage for their use.

The limitations of our study include its retrospective nature and the relatively small population size. Nevertheless, the influence of obesity on the response to CCBs appears to be of the magnitude that was evident even using a small sample size and the variability inherent in this type of study. The disease severity, degree of obesity, and inconsistency in corticosteroid dosing may have further contributed to the variability in drug response. A larger prospective clinical trial in which drug therapy and response measures are standardized should be carried out to confirm our results.

In conclusion, obesity and corticosteroid therapy are important confounding factors that govern the responsiveness of pediatric patients treated for renal disease with antihypertensive drugs. Obesity should be considered when initiating antihypertensive drug therapy for children with kidney disease.

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References

1. Spurgeon D (2002) Childhood obesity in Canada has tripled in past 20 years. Br Med J 324:1416
2. Ogden CL, Carroll MD, Flegal KM (2003) Epidemiologic trends in overweight and obesity. Endocrinol Metab Clin North Am 32:741–760
3. Ogden CL, Flegal KM, Carroll MD, Johnson CL (2002) Prevalence and trends in overweight among US children and adolescents, 1999–2000. JAMA 288:1728–1732

4. Tremblay MS, Willms JD (2000) Secular trends in the body mass index of Canadian children. Can Med Assoc J 163:1429–1433
5. Hanevold CD, Ho PL, Talley L, Mitsnefes MM (2005) Obesity and renal transplant outcome: a report of the North American pediatric renal transplant cooperative study. Pediatrics 115: 352–356
6. Krebs NF, Himes JH, Jacobson D, Nicklas TA, Guilday P, Styne D (2007) Assessment of child and adolescent overweight and obesity. Pediatrics 120[Suppl 4]:S193–228
7. Sbarbati A, Osculati F, Silvagni D, Benati D, Galie M, Camoglio FS, Rigotti G, Maffeis C (2006) Obesity and inflammation: evidence for an elementary lesion. Pediatrics 117:220–223
8. Das UN (2001) Is obesity an inflammatory condition? Nutrition 17:953–966
9. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB (1999) Elevated C-reactive protein levels in overweight and obese adults. JAMA 282:2131–2135
10. Visser M (2001) Higher levels of inflammation in obese children. Nutrition 17:480–481
11. Visser M, Bouter LM, McQuillan GM, Wener MH, Harris TB (2001) Low-grade systemic inflammation in overweight children. Pediatrics 107:E13
12. Reinehr T, Stoffel-Wagner B, Roth CL, Andler W (2005) High-sensitive C-reactive protein, tumor necrosis factor alpha, and cardiovascular risk factors before and after weight loss in obese children. Metabolism 54:1155–1161
13. Hanafy S, Dagenais NJ, Dryden WF, Jamali F (2008) Effects of angiotensin II blockade on inflammation-induced alterations of pharmacokinetics and pharmacodynamics of calcium channel blockers. Br J Pharmacol 153:90–99
14. Sattari S, Dryden WF, Eliot LA, Jamali F (2003) Despite increased plasma concentration, inflammation reduces potency of calcium channel antagonists due to lower binding to the rat heart. Br J Pharmacol 139:945–954
15. Abernethy DR, Schwartz JB (1988) Verapamil pharmacodynamics and disposition in obese hypertensive patients. J Cardiovasc Pharmacol 11:209–215
16. Mayo PR, Skeith K, Russell AS, Jamali F (2000) Decreased dromotropic response to verapamil despite pronounced increased drug concentration in rheumatoid arthritis. Br J Clin Pharmacol 50:605–613
17. Neuhaus TJ, Ruth EM, Kemper M (2007) Obesity and other clinical endpoints in steroid-sensitive nephrotic syndrome. Pediatr Nephrol 22:471; author's reply 22:472–473
18. Weisinger JR, Kempson RL, Eldridge FL, Swenson RS (1974) The nephrotic syndrome: a complication of massive obesity. Ann Intern Med 81:440–447
19. Hadtstein C, Schaefer F (2008) Hypertension in children with chronic kidney disease: pathophysiology and management. Pediatr Nephrol 23:363–371
20. Biasucci LM, Liuzzo G, Fantuzzi G, Caligiuri G, Rebuzzi AG, Ginnetti F, Dinarello CA, Maseri A (1999) Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. Circulation 99:2079–2084
21. Flynn JT, Pasko DA (2000) Calcium channel blockers: pharmacology and place in therapy of pediatric hypertension. Pediatr Nephrol 15:302–316
22. von Vigier RO, Franscini LM, Bianda ND, Pfister R, Casaulta Aebischer C, Bianchetti MG (2001) Antihypertensive efficacy of amlodipine in children with chronic kidney diseases. J Hum Hypertens 15:387–391
23. Seeman T, Dusek J, Vondrak K, Flogelova H, Geier P, Janda J (2004) Ramipril in the treatment of hypertension and proteinuria in children with chronic kidney diseases. Am J Hypertens 17: 415–420
24. American Medical Association (2006) Physician ICD-9-CM 2006: International Classification of Diseases, 9th revision. Clinical modification. American Medical Association, Chicago
25. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, Flegal KM, Guo SS, Wei R, Mei Z, Curtin LR, Roche AF, Johnson CL (2000) CDC growth charts: United States. Adv Data:1–27
26. Task Force Report on High Blood Pressure in Children and Adolescents (2004) The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 114:555–576
27. National High Blood Pressure Education Program (1996) Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: a working group report from the National High Blood Pressure Education Program. National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Pediatrics 98:649–658
28. Campbell M (2004) Multiple logistic regression models—what are they? Midwifery 20:236–239
29. Abernethy DR, Schwartz JB, Todd EL, Luchi R, Snow E (1986) Verapamil pharmacodynamics and disposition in young and elderly hypertensive patients. Altered electrocardiographic and hypotensive responses. Ann Intern Med 105:329–336
30. Garanty-Bogacka B, Syrenicz M, Syrenicz A, Gebala A, Lulka D, Walczak M (2005) Serum markers of inflammation and endothelial activation in children with obesity-related hypertension. Neuro Endocrinol Lett 26:242–246
31. Foster BJ, Shults J, Zemel BS, Leonard MB (2006) Risk factors for glucocorticoid-induced obesity in children with steroid-sensitive nephrotic syndrome. Pediatr Nephrol 21:973–980
32. Walker BR, Edwards CR (1994) New mechanisms for corticosteroid-induced hypertension. Br Med Bull 50:342–355
33. Pirpiris M, Sudhir K, Yeung S, Jennings G, Whitworth JA (1992) Pressor responsiveness in corticosteroid-induced hypertension in humans. Hypertension 19:567–574
34. Erzen B, Sabovic M, Poredos P, Sebestjen M, Keber I, Simcic S (2006) Inflammation markers in young post-myocardial patients exhibiting various expressions of classic coronary risk factors. Coron Artery Dis 17:325–330
35. Mann DL (2002) Inflammatory mediators and the failing heart: past, present, and the foreseeable future. Circ Res 91:988–998
36. Gugler R, Shoeman DW, Huffman DH, Cohlmia JB, Azarnoff DL (1975) Pharmacokinetics of drugs in patients with the nephrotic syndrome. J Clin Invest 55:1182–1189
37. Keller F, Maiga M, Neumayer HH, Lode H, Distler A (1984) Pharmacokinetic effects of altered plasma protein binding of drugs in renal disease. Eur J Drug Metab Pharmacokinet 9:275–282
38. Gatti G, Perucca E, Frigo GM, Notarangelo LD, Barberis L, Martini A (1984) Pharmacokinetics of prednisone and its metabolite prednisolone in children with nephrotic syndrome during the active phase and in remission. Br J Clin Pharmacol 17:423–431
39. Clements JD, Jamali F (2007) Pravastatin reverses the down-regulating effect of inflammation on beta-Adrenergic receptors: a disease-drug interaction between inflammation, pravastatin, and propranolol. Vascul Pharmacol 46:52–59
40. Daneshtalab N, Lewanczuk RZ, Russell A, Jamali F (2004) Rheumatoid arthritis does not reduce the pharmacodynamic response to valsartan. J Clin Pharmacol 44:245–252
41. Daneshtalab N, Lewanczuk RZ, Russell AS, Jamali F (2006) Drug-disease interactions: losartan effect is not downregulated by rheumatoid arthritis. J Clin Pharmacol 46:1344–1355
42. Dagenais NJ, Jamali F (2005) Protective effects of angiotensin II interruption: evidence for antiinflammatory actions. Pharmacotherapy 25:1213–1229
43. Robinson RF, Nahata MC, Batisky DL, Mahan JD (2005) Pharmacologic treatment of chronic pediatric hypertension. Paediatr Drugs 7:27–40