

# Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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## **Hypothesis: $\beta$ -Adrenergic Receptor Blockers and Weight Gain : A Systematic Analysis**

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*Hypertension* 2001;37;250-254

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 72514

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## $\beta$ -Adrenergic Receptor Blockers and Weight Gain A Systematic Analysis

Arya M. Sharma, Tobias Pischon, Sandra Hardt, Iris Kunz, Friedrich C. Luft

**Abstract**—One of the arguments put forward against the primary use of  $\beta$ -blockers has been concern about adverse metabolic effects, such as unfavorable effects on lipids or insulin sensitivity. Another less-appreciated potential drawback is their propensity to cause weight gain in some patients. In 8 evaluable prospective randomized controlled trials that lasted  $\geq 6$  months, body weight was higher in the  $\beta$ -blocker than in the control group at the end of the study. The median difference in body weight was 1.2 kg (range  $-0.4$  to 3.5 kg). A regression analysis suggested that  $\beta$ -blockers were associated with an initial weight gain during the first few months. Thereafter, no further weight gain compared with controls was apparent. There was no relationship between demographic characteristics and changes in body weight. Based on these observations, the first-line use of  $\beta$ -blockers in obese hypertensive patients should be reviewed. Obesity management in overweight hypertensive patients may be more difficult in the face of  $\beta$ -blocker treatment. (*Hypertension*. 2001;37:250-254.)

**Key Words:** obesity ■  $\beta$ -blockers ■ body weight ■ hypertension, obesity

$\beta$ -Blockers have been used for the treatment of hypertension for decades and have been shown to decrease cardiovascular morbidity and mortality rates in patients with essential hypertension. Traditionally,  $\beta$ -blockers have been recommended as the first-line therapy for young patients with uncomplicated hypertension.<sup>1</sup> In these patients, hypertension is often characterized by a high sympathetic tone and increased cardiac output.<sup>2</sup> In contrast, the initial use of  $\beta$ -blockers in other patient groups, including patients with diabetes mellitus<sup>3</sup> and the elderly,<sup>4</sup> is less well established. One of the arguments put forward against the primary use of  $\beta$ -blockers has been concern about adverse metabolic effects on the lipid profile or on insulin sensitivity.<sup>5,6</sup> Another less-appreciated side effect is the propensity to cause weight gain.<sup>7</sup> Overweight is now well recognized as an important predictor of overall death.<sup>8,9</sup> Increased body weight is a clinical problem in the vast majority of hypertensive patients and almost all type 2 diabetic hypertensive patients.<sup>9</sup> Drugs that either promote weight gain or make it difficult for patients to lose weight are therefore of obvious concern in the obese hypertensive patient. Although findings on the relationship between  $\beta$ -blockade and weight gain can be found in the literature, most clinicians are apparently unaware of this side effect. Furthermore, this potential drawback is not discussed in any of the current management guidelines. We propose that  $\beta$ -blockers regularly produce weight gain. The magnitude and relevance of this effect remain to be determined.

### Magnitude of $\beta$ -Blocker–Associated Weight Gain

In a systematic search of the PubMed database<sup>10</sup> for English-language articles published between 1966 and 1999 using the terms “adrenergic-beta-antagonists,” “hypertension,” and “randomized clinical trials,” we identified 273 articles on randomized controlled clinical trials. Unfortunately, only 8 studies were of at least 6 months’ duration and included information about the patients’ body weight at both the start and the end of the trial. This finding is alone noteworthy. The propensity of  $\beta$ -blockers to cause weight gain has been known for years.<sup>11,12</sup> Obesity is one of the best known risk factors for the development of hypertension and other components of the metabolic syndrome.<sup>8</sup> Nevertheless, most investigators apparently were either oblivious of these facts or did not deem them worthy of mention.

The characteristics and changes in body weight in the selected studies are summarized in Table 1. Together, these trials included a total of 7048 patients, of whom 3205 received  $\beta$ -blocker therapy. The patients were followed over time periods that ranged from 6 months to 10 years. In 7 of the 8 trials, body weight was greater in the  $\beta$ -blocker group than in the control group at the end of the study (Figure 1). The median difference in weight between the  $\beta$ -blocker and control groups was 1.2 kg (range  $-0.4$  to 3.5 kg). There was no relationship between any demographic characteristic and the  $\beta$ -blocker–induced change in body weight. Thus, all patients appeared susceptible to weight gain when they received a  $\beta$ -blocker.

Received July 10, 2000; first decision July 31, 2000; revision accepted August 16, 2000.

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TABLE 1. Data From Randomized Trials Reporting Before- and After-Treatment Body Weight

Reference	Year	Follow-Up, mo	n	Weight Change, kg			
				Control		$\beta$ -Blocker	
Foss et al <sup>43</sup>	1990	6	104	Captopril	-0.3	Metoprolol	0.5
The Treatment of Mild Hypertension Research Group <sup>44</sup>	1991	12	802	Placebo	-4.5	Acebutolol	-4.3
				Amlodipine	-5.0		
				Chlorthalidone	-5.6		
				Doxazosin	-3.9		
				Enalapril	-5.3		
Davis et al <sup>12</sup>	1992	6	169	Placebo	-0.5	Atenolol	0.3
				Chlorthalidone	-1.9		
		12	169	Placebo	-0.5	Atenolol	0.6
				Chlorthalidone	-1.4		
		18	169	Placebo	-1.0	Atenolol	1.2
				Chlorthalidone	-0.7		
24	169	Placebo	-0.4	Atenolol	0.6		
		Chlorthalidone	-0.3				
Rössner et al <sup>7</sup>	1990	12	3327	Placebo	1.2	Propranolol	2.3
		24	1893		1.6	Propranolol	3.0
Schiffrin et al <sup>42</sup>	1994	12	17	Cilazapril	-2.0	Atenolol	$\pm 0$
	1996	24	17		-2.0	Atenolol	1.5
HAPPY and MAPH Trials <sup>11,48</sup>	1987/1988	12	5899	Bendroflumethazide or hydrochlorothiazide, plus hydralazine, spironolactone, and optional drug	-0.2	Atenolol or metoprolol	0.7
		45	6422		0.1	Atenolol or Metoprolol	1.1
		50	3234		-0.1	Metoprolol	1.5
UKPDS <sup>40,41</sup>	1994/1998	12	242	Captopril	0.5	Atenolol	1.5
		24	242		0.7	Atenolol	2.3
		102	758		1.6	Atenolol	3.4
Berglund et al <sup>49</sup>	1986	120	76	Bendroflumethazide	-0.2	Propranolol	-0.6

### Time Course of $\beta$ -Blocker–Associated Weight Gain

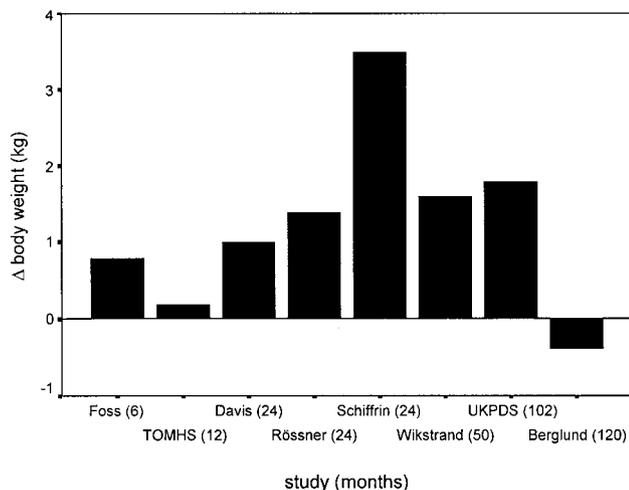
Apart from the magnitude, the time course of the body weight increase is of interest to both physicians and their patients. There are 3 possible weight gain patterns (Figure 2). However, a weighted regression analysis (Figure 3) showed that  $\beta$ -blocker consumption was associated with an initial weight gain in the first few months. Thereafter, no further weight gain, compared with controls, was apparent. Thus, the study duration did not further increase the difference in body weight between the  $\beta$ -blocker and control groups. Instead, short-term studies showed weight gains similar to those of longer studies. The analysis corroborates observations made in studies that did not meet our entry criteria.<sup>13,14</sup>

### Potential Mechanisms

The effects on body weight can be in large part explained by changes in energy metabolism (Table 2). Several investigators have shown that total energy expenditure may be reduced 4% to 9% with  $\beta$ -blocker treatment.<sup>15–20</sup> In a recent study, we showed that  $\beta$ -blockade reduces the basal metabolic rate by 12% in obese hypertensive patients, compared with obese

hypertensive patients receiving other antihypertensive agents.<sup>21</sup> Astrup et al<sup>22</sup> provided evidence for a  $\beta_2$ -adrenergic receptor–mediated facultative thermogenic component in skeletal muscle and a  $\beta_1$ -adrenergic receptor–mediated component in nonmuscle tissue. Furthermore, several investigators reported a 25% reduction in the thermogenic response to a mixed or carbohydrate-enriched meal after  $\beta$ -blockade.<sup>22,23</sup> Consistent with this finding,  $\beta$ -blockade also reduced the meal-induced increase in forearm oxygen consumption by 23%.<sup>22</sup> Interestingly, inhibition of sympathetic activity with the centrally acting agent clonidine also resulted in a 33% reduction in the thermogenic response to food.<sup>24</sup> Although the thermogenic effect of food accounts for only a relatively small proportion of daily energy expenditure (3% to 10%), small differences in thermogenic effect of food over longer periods of time may significantly contribute to the development and/or maintenance of obesity.<sup>25</sup>

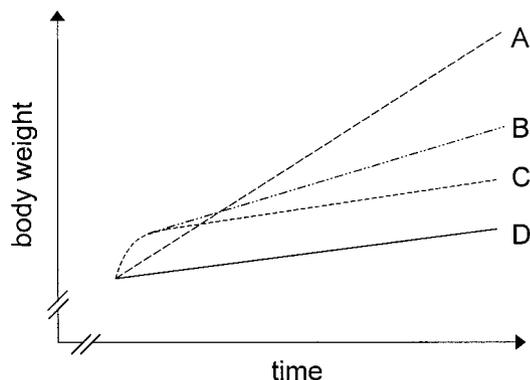
Apart from their direct metabolic effects,<sup>12</sup>  $\beta$ -blockers may also have a negative impact on total energy expenditure by increasing feelings of tiredness and decreasing anxiety. Such effects reduce so-called purposeless movement, or “fidgeting.” This non-exercise-associated thermogenesis (NEAT)



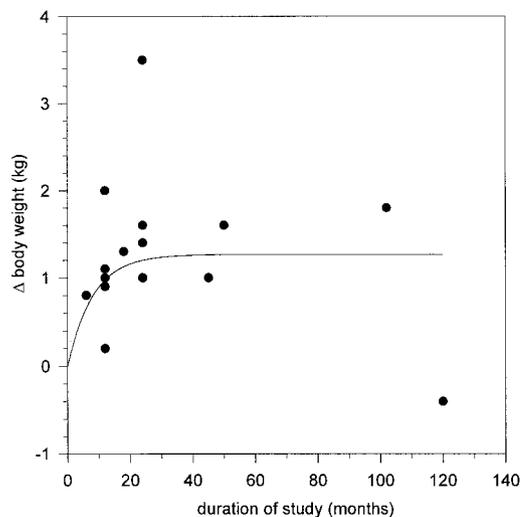
**Figure 1.** Weight gain on  $\beta$ -blocker therapy compared with control.

was recently shown to play a major role in the metabolic response to overeating. A low NEAT has been associated with remarkable weight gains in normal individuals.<sup>26</sup>  $\beta$ -Blockers also have negative effects on maximal and submaximal exercise capacity, which should be considered when prescribing  $\beta$ -blockers to physically active hypertensive patients.<sup>27</sup>

Together, these effects of  $\beta$ -blockers reduce total energy expenditure by only 5% or 10%, which corresponds to 100 to 200 kcal/d. However, this reduction could easily account for the 1- to 3.5-kg weight gain observed in clinical studies. A constant reduction in energy expenditure will not be associated with a continuing weight gain. Instead, an energy expenditure reduction unaccompanied by an energy intake reduction will result in weight gain until the positive energy balance is neutralized by the increased metabolic demand of increased tissue mass.<sup>28</sup> This result is consistent with the observation that weight gain is apparent during the early months of  $\beta$ -blockade. Thus, patients will achieve and maintain a new steady state at a higher body weight that counteracts the reduction in energy expenditure attributable to



**Figure 2.** Possible courses of weight gain over time under  $\beta$ -blocker therapy. A, Assuming a continuous increase in body weight under  $\beta$ -blocker therapy. B, Assuming an initial increase that becomes weaker with time. C, Assuming an initial increase that reaches a steady state with time. D, Normal weight gain over time.



**Figure 3.** Weight gain on  $\beta$ -blocker therapy compared with control in relationship to study duration. Weighted regression analysis of the trial data [ $y=a(1-e^{-bx})$   $a=1.266$  (95% CI 1.043 to 1.488),  $b=0.123$  (0.039 to 0.208),  $R^2=0.23$ ].

$\beta$ -blockade. In this context,  $\beta_3$ -adrenergic agonists are currently under clinical investigation for use as antiobesity agents.<sup>29</sup>

The ability to lose weight is obviously directly dependent on the ability to mobilize fat stores. However,  $\beta$ -blockade is also known to inhibit lipolysis in response to adrenergic stimulation.<sup>30</sup> Thus, systemic  $\beta$ -blockade may promote weight gain at least in part by inhibiting  $\beta$ -agonist-induced lipolysis. This feature would make it more difficult for individuals to lose weight under  $\beta$ -blockade.

### Individual Susceptibility

Although the mean 1-kg change in body weight does not seem impressive, individual susceptibility to  $\beta$ -blocker-induced weight gain may be quite variable. In Pima native Americans, weight gain has been related to the presence of genetic  $\beta$ -adrenergic receptor variants that may be associated with reduced metabolic rate.<sup>31</sup> Other investigators have also reported association between adrenergic receptor polymorphisms and body weight.<sup>32–35</sup> It would be of interest to determine whether these individuals are more likely to gain weight under  $\beta$ -blockade. Furthermore, because the sympathetic and thermogenic responses to food have been shown to decrease with age,<sup>36</sup> the weight gain-promoting effect of

**TABLE 2. Potential Mechanisms of  $\beta$ -Blocker-Associated Weight Gain**

Reduction in resting energy expenditure
Reduction in the thermic effect of food
Reduction in exercise tolerance
Increase in tiredness
Reduction in nonexercise thermogenesis
Inhibition of lipolysis
Exacerbation of insulin resistance

$\beta$ -blockers may be more pronounced in younger than in older individuals.

### Clinical Significance

Obesity is an important independent risk factor for cardiovascular disease. The risk is mainly associated with the presence of central or abdominal obesity.<sup>37</sup> The effect of  $\beta$ -blockers on fat distribution was not reported in any study. However,  $\beta$ -blockers may selectively promote the accumulation of abdominal fat, which is more sensitive to catecholamines than peripheral fat.<sup>38</sup> Thus, relatively small absolute changes in body weight may be associated with marked relative changes in abdominal fat depots, thereby contributing to the abnormalities related to carbohydrate and lipid metabolism. The propensity of  $\beta$ -blockers to interfere with carbohydrate metabolism and increase triglyceride concentrations while reducing HDL cholesterol is well known and has been discussed extensively elsewhere.<sup>5,6</sup> Because these traits are present in the vast majority of obese hypertensive patients,  $\beta$ -blockers could have a particular negative impact on this subgroup.

### Potential Management Implications

What is the implication of these findings? Neither the World Health Organization-International Society of Hypertension<sup>39</sup> nor the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure<sup>1</sup> makes specific recommendations for the pharmacological treatment of the obese hypertensive patients. We believe that  $\beta$ -blockers have important absolute indications, including the presence of ischemic heart disease and cardiac arrhythmias. However, in obese hypertensive patients without these conditions, alternatives, including ACE inhibitors and diuretics, should be preferred as a first-line therapy. This notion is supported by the observation in our analysis that ACE inhibitors were associated with less weight gain<sup>40,41</sup> or even weight loss.<sup>42–44</sup> Furthermore, a recent report suggests that ACE inhibition may significantly reduce the incidence of type 2 diabetes.<sup>45,46</sup> In contrast, a recent prospective study of antihypertensive therapy in 12 550 nondiabetic hypertensive adults showed a 28% increased risk of developing type 2 diabetes in persons receiving  $\beta$ -blockers.<sup>47</sup> This increased risk was independent of weight gain.

### Areas for Future Research

Overweight and obesity accompany hypertension in most patients. Nevertheless, evidence of the role of  $\beta$ -blockers in the management of the obese hypertensive patients or information on other drugs for that matter is scarce. There is a paucity of physiological studies that investigate the effects of  $\beta$ -blockers on metabolism in fat and muscle. Apart from the fact that there are no studies with hard end points that compare the protective effect of  $\beta$ -blockers with other medications in obese hypertensive individuals, there are few data on the efficacy and tolerability of  $\beta$ -blockers in these patients. Few studies have specifically addressed the issue of weight gain in terms of morbidity and quality of life. Furthermore, there are no data that compare the effects of selective and nonselective  $\beta$ -blockers on parameters of energy metabolism

in obese individuals. A substantial portion of sympathoadrenally mediated thermogenesis is probably mediated by atypical  $\beta_3$ -adrenergic receptors. There is little information on the effects of various  $\beta$ -blockers used for antihypertensive treatment on  $\beta_3$ -adrenergic receptor-mediated energy expenditure. Genetic variants of  $\beta_3$ -adrenergic receptors may also be important in this regard.

In summary, we find that effects on body weight are generally ignored in randomized studies of antihypertensive medication. The available evidence indicates that  $\beta$ -blocker treatment is often associated with a 0.5- to 3.5-kg increase in body weight after 6 to 12 months of treatment compared with other antihypertensive agents. When  $\beta$ -blockers are specifically indicated, the drugs should be given regardless of the effects on body weight. However, our data imply that weight control under  $\beta$ -blockade may be more difficult and requires greater attention from the patient, the nutritionist, and the physician.

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