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ORIGINAL ARTICLE

Effect of web-based lifestyle modification on weight control: a meta-analysis

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Objective: Web-based treatment programs are attractive in primary care because of their ability to reach numerous individuals at low cost. Our aim of this meta-analysis is to systematically review the weight loss or maintenance effect of the Internet component in obesity treatment programs.
Methods: MEDLINE and EMBASE literature searches were conducted to identify studies investigating the effect of Web-based individualized advice on lifestyle modification on weight loss. Randomized controlled trials that consisted of a Web-user experimental and non-Web user control group were included. Weight changes in the experimental group in comparison with the control group were pooled with a random-effects model.
Results: A total of 23 studies comprising 8697 participants were included. Overall, using the Internet had a modest but significant additional weight-loss effect compared with non-Web user control groups (−0.68 kg, $P=0.03$). In comparison with the control group, stratified analysis indicated that using the Internet as an adjunct to obesity care was effective (−1.00 kg, $P<0.001$), but that using it as a substitute for face-to-face support was unfavorable (+1.27 kg, $P=0.01$). An additional effect on weight control was observed when the aim of using the Internet was initial weight loss (−1.01 kg; $P=0.03$), but was not observed when the aim was weight maintenance (+0.68 kg; $P=0.26$). The relative effect was diminished with longer educational periods (P-trend = 0.04) and was insignificant (−0.20 kg; $P=0.75$) in studies with educational periods of 12 months or more.
Conclusion: The current meta-analysis indicates that the Internet component in obesity treatment programs has a modest effect on weight control. However, the effect was inconsistent, largely depending on the type of usage of the Internet or the period of its use.
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Keywords: Internet; lifestyle modification; weight control; meta-analysis; adult

Introduction

The numbers of overweight people are rising globally, and more than one billion adults have a body mass index (BMI) greater than 25 kg m^{-2} (ref. 1). In terms of combating this obesity epidemic and preventing various obesity-related diseases, it is essential to establish a healthcare system to facilitate self-management of obesity over the course of a lifetime. Face-to-face tailored lifestyle modification programs for treatment of obesity, which mainly consist of controlling dietary intake and increasing physical activity, are known to produce significant weight loss.[2–5] However, numerous barriers hinder the implementation of these programs. Most obese people have little chance to make use of professional help for weight management because of clinicians not referring patients for professional help, financial costs that are seldom covered by medical insurance and lack of time for frequent visits.[6,7] Moreover, most primary care practitioners offer insufficient lifestyle education in contrast to frequent prescription of medications[8] because of inadequate training in behavioral counseling, not dedicating sufficient time for counseling during the typical outpatient visit, and additional labor costs for staffing.[9]

Remote healthcare programs using the Internet have the potential to overcome some of these barriers and are expected to have a supplemental role or serve as an

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alternative in obesity care through promoting lifestyle modifications. Along with the growing penetration of Internet use worldwide, such programs have the ability to provide information to numerous individuals at a relatively low cost and with high anonymity.[10] Moreover, the Internet makes it possible for people to seek advice or communicate with a healthcare professional at any time, unlike use of a telephone.

Studies that evaluated the effectiveness of Web-based interventions on weight loss or maintenance before April 2008 were previously reviewed.[11] Unfortunately, some studies included in that review provided Web-based education to both control and experimental groups, although the intensity of the intervention differed between the two groups. However, inclusion of such studies would have failed to clarify the additional effect of an Internet component on weight control. Moreover, that review did not sufficiently explore the aspects of use of the Internet that could modify the relative weight-loss effect because of the limited number of studies included in the review.

The aim of this meta-analysis is to systematically review the weight-loss or weight-maintenance effect of an Internet component in obesity treatment programs for overweight or obese participants, and to specify characteristics of programs that could enhance the weight-loss effect.

Methods

Search strategy

Electronic literature searches (MEDLINE (between 1980 and 2011 April 2) and EMBASE (between 1980 and 2011 April 2)) were conducted to identify studies investigating the effect of Internet-based lifestyle instruction on weight control, using the following keywords related to the Internet (combined the Medical Subject Headings (MeSH) term (Internet) and the following text words (Internet OR Web or computerized or Web-based)) and obesity (combined MeSH terms (body mass index or body weight or overweight or obesity) and the following text words (body mass index or overweight or obes* or weight gain* or Weight change* or weight loss*). We examined reference lists of those publications to identify additional studies suitable for our purpose. We considered articles published in any language.

Studies were included if (1) they were randomized controlled trials using a parallel design; (2) all participants were adults who were designated as overweight or obese by the study-specific definition; (3) they consisted of a Web-user experimental group and non-Web user control group; (4) the intervention included controlling dietary intake and increasing physical activity; (5) the aim of using the Internet was initial weight loss or weight maintenance; and (6) the effect was assessed by absolute body-weight change. In one study,[12] although overweight or obesity was not clearly defined, we considered all the participants to be overweight or obese, because all of the participants had achieved a 10% weight reduction from their body weight as measured within 2 years of the beginning of the treatment of obesity; moreover, that study excluded subjects with a low BMI.

In addition to these inclusion criteria, the Internet must have a role either as a supplemental tool (that is, the obesity treatment program in the experimental group is the same as that in the control group except for additional support provided by the Web-based program) or as a substitute (that is, content of the Web-based obesity treatment program provided to the experimental group is similar to the in-person obesity care provided to the control group).

The intervention was considered as Web-based if participants in the experimental group received individualized (that is, not standardized) instruction, support for self-monitoring of physical activity and dietary intake, or counseling with the providers via the Internet. Studies were excluded if participants who were assigned to control groups used Internet websites for any purpose other than obtaining standard non-personalized information. Three of our investigators (SK, CH and ET) independently reviewed all relevant articles and identified eligible studies. Discrepancies were solved by the decision of another author (HS).

Data abstraction

We extracted the following data from each publication: publication year, country where the study was conducted, number of participants assigned to each experimental and control group, intervention period, mean age, percentage of women, percentage of Whites, mean BMI, dropout rate, aim of weight control (that is, weight loss or weight maintenance), whether intent-to-treat analysis was used, whether methods of randomization and compliance were described and summary of the educational program for both the experimental and control groups.

Data synthesis

The net effect size on weight loss in the experimental group compared with the control group was calculated by subtracting the change from baseline to final body weight in the control group from that in the experimental group. Standard error (SE) of the weight change was directly extracted from the report data or estimated from *P*-values or SEs of the baseline and final weight, assuming a correlation of 0.5 between the baseline and final measures within each group according to Follmann *et al.*[13] as follows:

$$SE = \sqrt{(SE_{\text{baseline}})^2 + (SE_{\text{final}})^2 - 2\times0.5\times(SE_{\text{baseline}})\times(SE_{\text{final}})}$$

To avoid double counting of the participants and maintain the independence across results from each randomized controlled trial, if studies had two or more experimental groups for one control group or two or more control groups for one experimental group, we calculated the mean effects of these groups using data on the number of participants, mean weight change and its corresponding standard deviation in each group. All effect sizes weighted by the square of their SE were pooled with a fixed- or random-effects model.[14] We used the results from the random-effects model if between-study heterogeneity, which was assessed by I^2,[15] was significant.

Analyses were repeated for subgroups into which studies were stratified based on the pre-specified key study characteristics. We also conducted meta-regression analyses to assess the influence of study characteristics on study results. Publication bias was assessed using two formal methods: Begg's rank correlation test[16] and Egger's asymmetry test.[17] A *P*-value of 0.05 or less was considered statistically significant. All analyses were carried out with STATA software version 11 (STATA Corporation, College Station, TX, USA).

Results

Details of study characteristics

Figure 1 shows details of the literature search. Our electronic literature search resulted in retrieval of 847 citations (426 from MEDLINE and 421 from EMBASE). Of these, 743 citations were excluded after the first screening. The remaining 104 articles and 10 additional articles identified by manual search were left for full-text review. After this review, 23 articles[12,18–39] met the inclusion criteria. In two of the 23 included studies,[25–26] two pairs of experimental and control groups were identified. Finally, 25 eligible trials comprising 8697 participants were analyzed in this meta-analysis.

Table 1 shows the summary of participants or study design characteristics of the 23 randomized controlled trials included in this meta-analysis. Intervention periods, including both educational and observational periods, ranged from 3–30 months. Only eight studies had intervention periods of 12 months or more. A large number of the included studies (16 studies) were conducted in the USA. In about half of the included studies (11 studies), participants were women-dominant (⩾80%). Study-level mean (±s.d.) age and BMI were 46 (±6) years and 32 (±3) $kg\,m^{-2}$, respectively. Of the 22 studies that provided the study-specific minimum BMI to define overweight or obesity, the value was $\geqslant 25\,kg\,m^{-2}$ to $< 30\,kg\,m^{-2}$ except in three studies[26,35,38] that used a BMI $<25\,kg\,m^{-2}$ cut-off value for being overweight and three studies[28,32,36] that exclusively targeted participants with a BMI $\geqslant 30\,kg\,m^{-2}$. Most of the studies (17 studies) used an intent-to-treat analysis. Mean (range) of the dropout rate was 17.8% (0–79.6%) and the reasons for dropping out were described in 12 studies. Methods of randomization were described in only seven studies, and participants' compliance was not mentioned in 11 studies.

Table 2 shows details of the obesity treatment programs in each included study. To summarize the study-specific Web-based programs in terms of the role of the Internet, 16 studies[18–20,23–24,26–28,30–31,33–36,38–39] used the Internet as an adjunct to the non-Web-based obesity care support provided in both control and experimental groups. One study[25] used it as a substitute for face-to-face counseling. The remaining six studies[12,21–22,29,32,37] investigated the effectiveness of the Internet as either an adjunct or substitute. In five studies, the aim of the lifestyle modification was weight maintenance, whereas it was initial weight loss in the remaining 18 studies.

In most studies (20 studies), participants received individualized instructions on the Website, and 14 studies included other content in addition to the instructions. Participants were instructed to record daily dietary intake

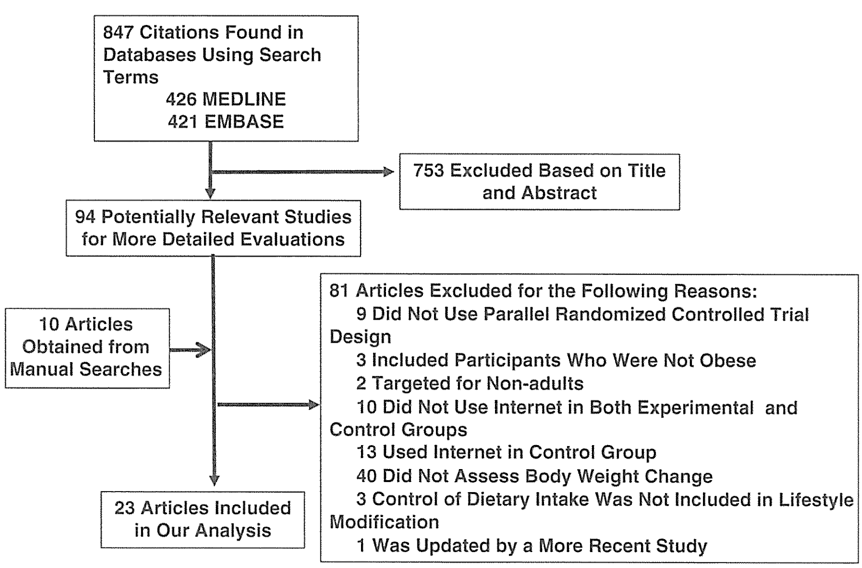

Figure 1 Flow chart of literature search for the meta-analysis.

Table 1 Details of participants or study-design characteristics of the 23 randomized controlled studies included in this meta-analysis

Study source		*No. exp*	*No. control*	*Country*
Wylie-Rosett et al.[20]	Included in-person counseling	194	97	USA
		183		
Harvey-Berino et al.[21]	Versus frequent support	30	32	USA
	Versus minimal support		28	
Harvey-Berino et al.[22]	Versus frequent support	77	77	USA
	Versus minimal support		78	
Womble et al.[23]		23	24	USA
Rothert et al.[24]		1475	1387	USA
Mobley et al.[25]	Included initial counseling	43	43	USA
		43	43	
Wing et al.[12]	Versus face to face	104	105	USA
	Versus minimal support		105	
Adachi et al.[26]	Included[a] self-monitoring[d]	36	53	Japan
		44	50	
Polzien et al.[27]		19[b]	19	USA
McConnon et al.[28]		111	110	UK
Svetkey et al.[29]	Versus personal support	348	342	USA
	Versus self-directed		342	
Cussler et al.[30]		66	69	USA
Hunter et al.[31]		222	224	USA
Digenio et al.[32]	Versus self-help	74	76	USA
	Versus phone contact		76	
	Versus face-to-face contact		74	
Patrick et al.[18]		33	32	USA
van Wier et al.[19]		464	460	Neth.
Morgan et al.[33]		34	31	UK
Ueki et al.[34]		13	17	Japan
Yoo et al.[35]		57	54	Korea
Bennete et al.[36]		51	50	USA
Harvey-Berino et al.[37]	Included in-person group meeting	162	158	USA
		161		
Tanaka et al.[38]		23	28	Japan
Christian et al.[39]		163	160	USA

Study source	*Educational (+observational) period, months*	*Mean age, years*	*% of women*	*Mean BMI kg m^{-2}*	*Minimum BMI for OW or OB, kg m^{-2}*
Wylie-Rosett et al.[20]	12	52.2	82.3	35.6	25
Harvey-Berino et al.[21]	18[c]	48.4	85.4	32.2	25
Harvey-Berino et al.[22]	18[c]	45.9	83.6	29.1	25
Womble et al.[23]	12	43.7	100	33.4	27
Rothert et al.[24]	1.5 (+4.5)	45.4	82.8	32.1	27
Mobley et al.[25]	6	33.1	36.6	31.9	28
Wing et al.[12]	18	51.3	63.2	28.6	ND
Adachi et al.[26]	1 (+6)	46.6	100	26.1	23
Polzien et al.[27]	3	41.4	100	33.1	25
McConnon et al.[28]	12	45.8	77.0	34.4	30
Svetkey et al.[29]	30	55.6	63.4	34.1	25
Cussler et al.[30]	12	48.2	100	30.7	25
Hunter et al.[31]	6	33.9	50.2	29.4	25
Digenio et al.[32]	6	44.0	86.3	34.5	30
Patrick et al.[18]	4	44.9	80.0	33.2	25
van Wier et al.[19]	6	43.0	34.2	29.6	25
Morgan et al.[33]	3	35.9	0.0	30.6	25
Ueki et al.[34]	3	55.9	40.0	29.1	25
Yoo et al.[35]	3	58.2	41.4	25.6	23
Bennete et al.[36]	3	54.4	52.5	34.6	30
Harvey-Berino et al.[37]	6	46.6	93.0	35.7	25
Tanaka et al.[38]	1 (+6)	46.0	0	26.2	23
Christian et al.[39]	6	49.6	68.4	34.3	25

Table 1 Continued

Study source	Dropout rate %	Used ITT analysis	Gave reason for dropping out	Description of compliance	Description of randomization
Wylie-Rosett et al.[20]	19.4	N	N	Y	Y
Harvey-Berino et al.[21]	26.2	N	N	N	N
Harvey-Berino et al.[22]	24.1	Y	Y	Y	N
Womble et al.[23]	34.0	Y	Y	Y	N
Rothert et al.[24]	79.6	N	N	N	N
Mobley et al.[25]	28.5	Y	N	N	N
Wing et al.[12]	7.3	Y	Y	Y	Y
Adachi et al.[26]	3.8	N	N	N	N
Polzien et al.[27]	10.5	Y	N	Y	N
McConnon et al.[28]	40.7	N	Y	Y	Y
Svetkey et al.[29]	6.6	Y	Y	Y	N
Cussler et al.[30]	17.8	Y	N	Y	N
Hunter et al.[31]	21.0	Y	Y	Y	N
Digenio et al.[32]	28.3	Y	Y	Y	Y
Patrick et al.[18]	16.7	Y	Y	N	N
van Wier et al.[19]	29.7	Y	Y	Y	Y
Morgan et al.[33]	16.9	Y	Y	N	Y
Ueki et al.[34]	0.0	N	N	N	N
Yoo et al.[35]	9.8	N	N	N	N
Bennete et al[36]	15.8	Y	Y	Y	N
Harvey-Berino et al.[37]	4.4	Y	Y	Y	Y
Tanaka et al.[38]	9.8	Y	N	N	N
Christian et al.[39]	5.7	Y	Y	N	N

Abbreviations: BMI, body mass index; ITT, intent to treat; N, No; ND, not described; No. exp, number of participants in experimental group; No. control, number of participants in control group; OB, obesity; OW, overweight; Y, Yes. [a]Participants were instructed to continue self-monitoring during follow-up period after intervention period. [b]We used data only on 'continuous technology group'. [c]Included 6-month similar weight-loss treatment period. [d]Self-monitoring means Web-based support for self-monitoring, but not self-monitoring itself. This is also true for Table 2.

or physical activity and submit this information in 14 studies. In nine studies, participants communicated with the lifestyle instructors via e-mail and nine studies included counseling through other methods (that is, face-to-face and using the phone), as well as the Internet program.

Overall effects of using the Internet on weight control

Figure 2 provides a forest plot showing the net effect of using the Internet on weight loss compared with not using it. Overall, using the Internet had a modest but significant additional weight-loss effect when compared with results in non-Web-user control groups (−0.68 kg, $P=0.03$). However, large and highly significant between-study heterogeneity was observed in the effect size (I^2, 84.4%; $P<0.001$). Publication bias was not statistically detected ($P=0.62$ for Begg's test and $P=0.79$ for Egger's test).

Sensitivity analysis

Table 3 shows results of stratified and meta-regression analyses across a number of key study characteristics to explore the origin of the between-study heterogeneity. On the whole, the additional weight-loss effect through use of the Internet seemed to be influenced by characteristics of the study design, such as the role or aim of use of the Internet, the period of its use and content of the Web-based program, rather than characteristics of the participants, (for example, mean age, mean BMI and geographic region) or BMI definition used for overweight or obesity.

In comparison with control groups, although a significantly favorable effect was observed when Internet support was added to the experimental group as an adjunct to the obesity care provided to all participants in an individual study (net effect (95% confidence interval (CI)) (kg), −1.00 (−1.57 to −0.43), $P=0.003$), an adverse effect was observed when the Internet was provided to the experimental group as a substitute for the face-to-face support similar to that given to the control group (net effect (95% CI) (kg), +1.27 (0.29–2.25), $P=0.01$). Although adding face-to-face support to Web-based support enhanced the weight-loss effect of using the Internet (net effect (95% CI) (kg), −1.93 (−2.71 to −1.15), $P<0.001$), the weight-loss effect was nonsignificant when face-to-face support was not provided (net effect (95% CI) (kg), −0.19 (−0.87 to 0.49), $P=0.59$). The difference between results with and without face-to-face support was significant ($P=0.003$).

In comparison with the non-Web user control group, the Web-based program was effective when the aim of using the Internet was initial weight loss (net effect (95% CI) (kg), −1.01 (−1.68 to −0.34), $P=0.03$), but was ineffective when the aim was weight maintenance (net effect (95% CI) (kg), 0.68 (−0.50 to 0.85), $P=0.26$).

Regarding the content of the Internet programs, content other than individualized instructions for behavioral

Table 2 Summary of obesity treatment programs provided to the experimental and the control groups in each study

Study source	*Educational program*			
	Experimental group programs via Internet	*Programs via other medium*	*Control group*	*Aim for weight control*
Wylie-Rosett *et al.*[20]	Instruction	With in-person counseling Without in-person counseling	Material	Loss
Harvey-Berino *et al.*[21]	Instruction, self-monitoring and counseling		Self-monitoring with in-person instruction and frequent counseling or only minimal.	Maintenance
Harvey-Berino *et al.*[22]	Instruction, self-monitoring and counseling		Self-monitoring with in-person instruction and frequent counseling or only minimal.	Maintenance
Womble *et al.*[23]	Instruction, self-monitoring and counseling	In-person counseling	Material, counseling	Loss
Rothert *et al.*[24]	Instruction		self-directed	Loss
Mobley *et al.*[25]	Counseling	Initial instruction with and without counseling	Counseling, initial instruction with and without counseling	Loss
Wing *et al.*[12]	Instruction and self-monitoring	Counseling	Instruction, self-monitoring (via phone or face-to-face) or only material	Maintenance
Adachi *et al.*[26]	Instruction	Material and self-monitoring	Material, with and without self-monitoring	Loss
Polzien *et al.*[27]	Self-monitoring	Instruction and counseling	Instruction and counseling	Loss
McConnon *et al.*[28]	Instruction and self-monitoring		Material	Loss
Svetkey *et al.*[29]	Instruction, self-monitoring and counseling		Counseling, self-monitoring or only material	Maintenance
Cussler *et al.*[30]	Instruction, self-monitoring and counseling		Self-directed	Maintenance
Hunter *et al.*[31]	Instruction, self-monitoring and counseling	Counseling via phone	Self-help	Loss
Digenio *et al.*[32]	Counseling	Material	Material with counseling (via phone or face-to-face) or only material	Loss
Patrick *et al.*[18]	Instruction	Counseling	Material	Loss
van Wier *et al.*[19]	Instruction and counseling	Material	Material	Loss
Morgan *et al.*[33]	Instruction and self-monitoring		Material	Loss
Ueki *et al.*[34]	Instruction and self-monitoring	Instruction via fax/mail and supplemental food (jelly)	Self-monitoring, and supplemental food (jelly)	Loss
Yoo *et al.*[35]	Instruction and self-monitoring		Outpatient practice	Loss
Bennete *et al.*[36]	Instruction	In-person counseling	Outpatient practice+material	Loss
Harvey-Berino *et al.*[37]	Instruction, self-monitoring, electronic material and online meeting (substitute for in person group meeting)	In-person group meeting (substitute for online meeting)	Material and self-monitoring, group meeting	Loss
Tanaka *et al.*[38]	Instruction	Material and self-monitoring	Material and self-monitoring	Loss
Christian *et al.*[39]	Instruction	Material and counseling	Material	Loss

Note: Material indicates printed information.

modification did not produce greater weight-loss effect compared with non-Web-based programs (−0.25 kg, $P=0.49$), with only individualized instructions on the Website being effective (net effect (95% CI) (kg), −1.33 (−2.32 to −0.34), $P=0.008$). Examples of such individualized instruction are support for self-monitoring of dietary intake and physical activity (−0.14 kg, $P=0.77$), and counseling via the Internet (−0.17 kg, $P=0.72$).

The relative weight-loss effect of the Internet component was not significantly affected by whether an intent-to-treat analysis was used ($P=0.95$) or whether the dropout rate was 20% or more ($P=0.28$). However, when educational periods were categorized into <6 months, 6 to <12 months and ⩾12 months, it was shown that the effect was diminished with longer educational periods (P-trend = 0.04). The weight-loss effect was insignificant (−0.20 kg; $P=0.75$) in studies with educational periods ⩾12 months, and was significant in studies with an educational period <6 months (−1.55 kg, $P=0.001$).

Discussion

The current meta-analysis indicated that the relative effect of the Internet component in the obesity programs was statistically significant. However, the amount of weight change was much more modest than that with use of anti-obesity drugs (for example, orlistat (−2.9 kg), sibutramine (−4.2 kg), rimonabant (−4.7 kg)[40]) and bariatric surgery (−39.7 kg).[41]

One reason for the modest effect of use of the Internet in weight-loss programs might be that obesity treatment programs had inappropriately used the Internet. The current stratified analyses indicated that those using the Internet as a substitute for face-to-face support experienced a smaller weight loss than the control group. Moreover, another finding from the stratified analyses was that the Web-based programs did not have a significant additional weight-loss effect unless their use was combined with face-to-face support. These results suggest that an in-person contact

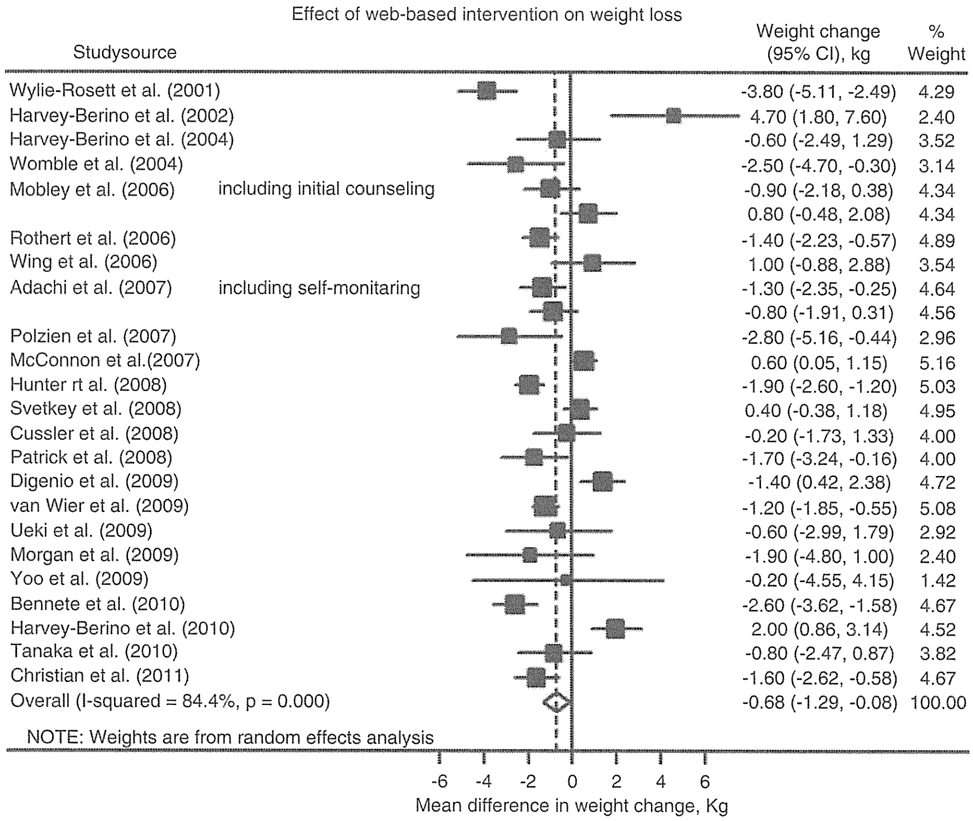

Figure 2 Forest plot showing the effect of Web-based weight-loss program on weight loss (Web-user experimental group versus non-Web-user control group). Size of squares reflects the statistical weight of each study. Overall effect size is indicated by unshaded diamond.

approach is superior to a technology-based approach from the viewpoint of the amount of weight loss; if used, an Internet program needs to include the component of a face-to-face program for participants to achieve weight loss.

It is known that social support is one of the important aspects of behavioral obesity treatment and is associated with better weight-loss outcomes.[42] One supposition for the superiority of face-to-face treatment is derived from the perception that the participants are supported by many staff members, as has been already suggested by a previous study.[37] It was reported that some participants felt uncomfortable using the Internet even when compliance in using the Internet for weight loss was maintained.[21] Another supposition is that this feeling of discomfort could cause participants to lose enthusiasm for weight loss and negatively influence the effectiveness of the Internet for this purpose.

However, as previously mentioned, the high cost that is inherent in providing human support for weight loss obviously represents a major barrier in clinical practice. A previous cost-to-benefit study reported that the deployment of obesity therapists increased the mean cost per pound weight reduction by $10.2, while the deployment of a computer network system increased it by only $2.3 [ref. 20]. Moreover, it is also obvious that a reduction in frequency of healthcare visits, as well as reduction in consultation time per visit, represent major strengths in Web-based healthcare compared with healthcare delivered by humans. Therefore, it is necessary that Web-based obesity-care programs become more widespread and are developed to result in greater weight-loss effect than the present Web-based systems. Ideally, they would achieve a weight-loss effect comparable to that of face-to-face support.

The long-term weight-loss effect seems to be one of the major problems in Web-based strategies, as is the case with many weight-control intervention studies. The current sensitivity analyses indicated that the additional weight-loss effect via the Internet was attenuated with a longer educational period. Additionally, the Web-based program was found not to be superior to other obesity treatment programs when its aim was to maintain body weight after a previous weight reduction. These results suggest that one of the major problems in using the Internet for weight loss appears to be long-term sustainability of the Internet program. Harvey-Berino *et al.*[21] reported that during a weight-loss intervention period more participants who were assigned to an Internet group lost enthusiasm than those assigned to an in-person support group. We speculate that Internet users acquire 'tolerance' to stimuli that text messages or e-mail communications give in the course of

Table 3 Stratified analyses of the effect of Web-based intervention on weight change

Variable	*Number of data*[a]	*Mean difference (95 % CI), kg*	I^2 (%)	*P-value for heterogeneity*	Significance*	*Meta-regression***
Total	25	−0.68 (−1.29 to −0.08)	84.4	<0.001	0.03	—
Mean age						
<45	16	−0.48 (−1.29 to 0.32)	85.8	<0.001	0.24	Referent
⩾45	9	−1.01 (−1.95 to −0.07)	81.2	<0.001	0.04	0.41
Mean BMI						
$<30\,kg\,m^{-2}$	9	−1.22 (−1.58 to −0.85)	25.3	0.22	<0.001	Referent
$\geqslant 30\,kg\,m^{-2}$	16	−0.61 (−1.46 to 0.25)	88.3	<0.001	0.17	0.75
Minimum BMI for determining overweight or obesity						
$<25\,kg\,m^{-2}$	4	−1.00 (−1.68 to −0.31)	0.0	0.89	0.004	0.95
$\geqslant 25$ to $<30\,kg\,m^{-2}$	17	−0.84 (−1.57 to −0.10)	83.0	<0.001	0.03	Referent[e]
$30\,kg\,m^{-2}$	3	−0.18 (−2.25 to 1.88)	94.5	<0.001	0.86	0.50
Not described	1	1.00 (−0.89 to 2.89)	—	—	0.30	0.31
% Women						
<80%	12	−0.82 (−1.58 to −0.07)	83.1	<0.001	0.03	Referent
⩾80%	13	−0.53 (−1.57 to 0.51)	86.4	<0.001	0.32	0.67
Country						
USA	17	−0.64 (−1.48 to 0.19)	87.5	<0.001	0.13	Referent
others	8	−0.70 (−1.50 to 0.09)	69.9	0.002	0.08	0.89
Educational period, months						
<6 months	9	−1.55 (−2.05 to −1.05)	10.6	0.35	0.001	Referent[e,f]
⩾6 to <12 months	8	−0.39 (−1.38 to 0.60)	89.0	<0.001	0.44	0.16
⩾12 months	8	−0.20 (−1.46 to 1.06)	87.1	<0.001	0.75	0.12
Was observational period included?						
No	23[b]	−0.61 (−1.16 to −0.05)	85.2	<0.001	0.03	Referent
Yes	6[b]	−1.05 (−1.47 to −0.64)	0.0	0.85	<0.001	0.45
Aim of using Internet						
Initial weight loss	20	−1.01 (−1.68 to −0.34)	85.2	<0.001	0.03	Referent
Weight maintenance	5	0.68 (−0.50 to 1.85)	61.9	0.03	0.26	0.03
Role of use of Internet						
Additional support	23[c]	−1.00 (−1.57 to −0.43)	79.2	<0.001	<0.001	Referent
Substitute for personal support	8[c]	1.27 (0.29 to 2.25)	73.7	<0.001	0.01	<0.001
Content of Web-based intervention						
1) Included other than instruction						
No	9	−1.33 (−2.32 to −0.34)	85.2	<0.001	0.008	Referent
Yes	16	−0.25 (−0.98 to 0.47)	81.0	<0.001	0.49	0.09
2) Included self-monitoring in addition to instruction						
No	12	−1.15 (−1.88 to −0.42)	81.9	<0.001	0.002	Referent
Yes	13	−0.14 (−1.06 to 0.79)	82.8	<0.001	0.77	0.11
3) Included e-mail counseling in addition to instruction						
No	10	−1.05 (−1.90 to −0.21)	85.0	<0.001	0.02	Referent
Yes	15	−0.17 (−1.09 to 0.75)	84.9	<0.001	0.72	0.17
Was in-person counseling added to Web-based intervention?						
No	17[d]	−0.19 (−0.87 to 0.49)	81.9	<0.001	0.59	Referent
Yes	9[d]	−1.93 (−2.71 to −1.15)	67.9	0.002	<0.001	0.003
Dropout rate						
<20%	15	−0.99 (−1.84 to −0.14)	81.6	<0.001	0.02	Referent
⩾20%	10	−0.28 (−1.19 to 0.63)	87.8	<0.001	0.54	0.28
Use of intention-to-treat analysis						
No	8	−0.63 (−1.89 to 0.604)	88.1	<0.001	0.34	Referent
Yes	17	−0.68 (−1.40 to 0.02)	82.9	<0.001	0.06	0.95

Abbreviation: BMI, body mass index; CI, confidence interval. **P*-values for significance of mean difference in weight change between experimental (Internet users) and control (non-Internet users) groups. ***P*-values for difference in weight change across strata. [a]Principally, data with the longest intervention period were used if two or more results were reported according to the observational (non-educational) period so that double counting was avoided. [b]Four data sets were added as both data on studies with and without an observational period were reported in three studies.[24,26,33] [c]Six data sets were added because two roles of the Internet as additional or alternative support were examined in six studies.[12,21–22,29,32,37] [d]In one study,[20] two different kinds of effects of the Internet with and without in-person counseling were examined. [e]Multivariate meta-regression analysis was conducted. [f]*P*-trend was 0.04 if the educational period was a categorical variable.

the Web-based educational program and become bored with these stimuli. This would make it difficult for participants to maintain their motivation for lifestyle modifications, which may diminish chances for success in weight control. It is suggested that Web-based lifestyle modifications should gradually become more intensive or should be combined with in-person support, especially when the aim is success in maintaining long-term weight loss.

According to the stratified analyses, it is possible that using the Internet for self-monitoring or counseling does not contribute to additional weight loss compared with Internet-based obesity care without such content. Actually, it has been suggested that self-monitoring or communication via the Internet does not motivate people to modify behavior for weight control. For example, barriers such as stress, lack of social support and discomfort with recording information have been reported with regard to self-monitoring systems.[43] It also has been reported that participants assigned to an Internet group often feel that they are unable to communicate effectively with their group members or therapists.[44] A key to improve the efficacy of Web-based weight-loss programs might be the development of Web-based instruction rather than self-monitoring or communication via the Internet. To make the instruction more attractive, the text messages should not be repetitious but novel and more thoughtful of the personalized aspects of behavioral therapy as if the Web-users would consider the automated messages the same as if they were given face-to-face.

Several limitations must be addressed in this meta-analysis. First, the current meta-analysis could detect only eight eligible studies with a duration $\geqslant$12 months, which accounted for about one third (8/23) of the included studies. Therefore, this analysis might not necessarily provide clinically sufficient evidence for the long-term effect of an Internet component on weight control. Second, in this type of randomized controlled trial, practically, a double-blinded method is impossible. The participants assigned to the control group might have felt a sense of competition with the Internet group, which could have created bias toward weakening the effect of the Web-based intervention. This type of bias has been referred to as the 'Avis effect'.[45] Third, poor compliance is recognized as a major issue in most online studies.[46] Actually, several studies have reported that compliance or levels of Internet usage were found to be associated with weight loss.[10,20,23,32,47–48] However, quite a few of the studies included in this meta-analysis did not provide information on compliance (for example, Website log-in frequency). Fourth, few studies have been conducted on Web-based weight-loss programs targeted exclusively for men, partly because of the fact that men are less interested in weight loss than women.[49]

We also suggest several issues that could be addressed by future research: (1) a cost-to-benefit ratio that involves, in addition to the amount of weight loss, the reduction in incidence and medical cost of obesity-related diseases, such as hypertension, diabetes, and furthermore, cardiovascular diseases as a benefit of obesity care; (2) the proper proportion of online and in-person obesity care support for maximizing the cost-to-benefit; and (3) the characteristics of obesity care (for example, standardized outpatient practice or self-help material) or of obese persons (for example, computer experience, health literacy and type of occupation) that can benefit from supplemental care using the Internet.

In conclusion, the Internet component in obesity treatment programs had a modest but significant effect on weight control compared with non-use of the Internet. However, the effect appears to depend on the usage of the Internet or the period of its use, rather than on participants' characteristics such as age or gender. Although an in-person approach is suggested to have a greater weight-loss effect than a Web-based approach, the development of technology-based programs should be continued from the viewpoint of saving time and cost, especially focusing on appropriate combinations of face-to-face and Web-based support, as well as making educational programs more attractive for participants.

Conflict of interest

The authors declare no conflict of interest.

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総　論

KeyWords
◎大規模臨床研究
◎腎症
◎網膜症
◎大血管症
◎人種差

日本人糖尿病患者の実態—JDCS

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Headline

1. 2型糖尿病の病態や合併症には人種差がみられるため，日本人患者の臨床エビデンスが求められてきた．Japan Diabetes Complications Study（JDCS）は，日本人2型糖尿病患者約2,000人を前向きに追跡してきた大規模臨床研究である．
2. 専門医に管理された糖尿病患者では，腎症の発症や増悪がこれまで考えられてきたより低く，患者の30%に腎症の寛解が認められた．また喫煙が腎症のリスクファクターであることが明らかになった．
3. 開始時HbA1c（JDS値）9%以上の患者では，ほぼ半数がその後8年間に網膜症を発症した．一方，7%未満であっても1割に網膜症の発症がみられ，予防にはかなり厳格な血糖コントロールを要することが判明した．
4. 8年間の無作為化比較試験により，通常の専門医診療に加え，生活習慣教育を強化した治療介入群において，脳卒中の発症が有意に抑制されていた．

JDCSの背景

合併症を抑制し患者のQOLと健康寿命を維持することは，糖尿病治療の最終目標であり，合併症の発症率やリスクファクターは治療対策上，重要な基礎資料である．一方，2型糖尿病においては，多因子遺伝と生活習慣の双方が発症・進展に強く関与するため，その病態や合併症には人種差や民族差がみられる．現代の糖尿病診療は，おもに欧米の大規模臨床研究のエビデンスによるところが大きいが，欧米の研究結果が，どの程度日本人患者に当てはまるかは明らかでなく，日本人糖尿病患者の大規模臨床エビデンスが求められてきた．

JDCSの概要

Japan Diabetes Complications Study（JDCS）[1]は，多数の日本人2型糖尿病患者を前向きに観察して日本人患者の病態や特徴を明らかにするとともに，生活習慣指導を中心とした強化治療介入の効果を検討することを目的として行われてきた．対象は全国の大学病院や総合病院など糖尿病専門施設59か所に通院する，進行合併症をもたない2型糖尿病患者2,033名（女性47%，平均年齢59歳）である．合併症の発症・進展をあらかじめ設けられた診断基準に基づき専門委員によって判定し，同時に血糖・血圧・血清脂質・生活習慣などについて，年1回の定期調査を行った．

腎症の発症率

腎症は，登録時に①試験紙法による蛋白尿陰性，②随時尿アルブミン・クレアチニン比（Alb/Cr比）連続2回150 mg/gCr以下，③尿沈渣正常，のすべてを満たした患者1,558人に

本稿では，HbA1cはJDS値で記載した（糖尿病53（6）;450-467, 2010）．

0370-999X/11/¥100/頁/JCOPY

ついて，発症率と発症リスクを前向きに検討した[2]．顕性腎症（尿Alb/Cr比300 mg/gCr以上）の発症率は，1,000人あたり年間6.7人で，このうち正常アルブミン尿（＜30 mg/gCr）からの発症率は1,000人あたり2.3人であった．これまで日本人をはじめとする東アジア人糖尿病患者は腎症を発症しやすいとされていたが[2〜5]，今回の結果は，イギリスのUnited Kingdom Prospective Diabetes Study（UKPDS）[6]における顕性アルブミン尿（300 mg/L）の発症率である年間約3%よりむしろ低く，初期から専門医に管理された糖尿病患者では，腎症の発症や増悪がかなり抑えられる可能性が示された．いわゆる心腎連関が，JDCS以外のわが国の糖尿病患者においても示されており[7]，大血管症予防の観点からも早期からの腎症の治療管理が重要である．一方，尿Alb/Crが30～150 mg/gCrの患者の30%に腎症の寛解（30 mg/gCr未満への正常化）が認められた．

腎症のリスクファクター

登録時の尿Alb/Crが30 mg/gCr未満の群に比べると，30～150 mg/gCrの群では，顕性腎症の発症リスクが8.5倍であった[2]（図1）．また，HbA1c 7%未満の群と比べると，7～9%未満の群の発症リスクは2.7倍，9%以上の群では5.8倍であった．また，収縮期血圧120 mmHg未満の群に比べて，120～140 mmHgの群の発症リスクは2.3倍，140 mmHg以上の群では3倍であった．さらに，喫煙は顕性腎症のリスクを約2倍に上昇させることも明らかになった．喫煙はすでに日本人2型糖尿病患者において，早期腎症発症のリスクを高めることも知られており[8]，喫煙の腎症の発症および進展に及ぼす悪影響が明らかになった．

網膜症の発症率

JDCSでは網膜症は，国際分類[9]により5段階（①なし，②軽度非増殖性，③中等度非増殖性，④重度非増殖性，⑤増殖性）に分類され，開始時において①であった1,221名，②であった410名を対象に，それぞれ発症と進展増悪について検討された[10]．毎年の眼底検査結果により，開始時に①の患者については②以上の段階に，開始時に②の患者については③以上の段階に，いずれも2年連続して分類された時点をそれぞれ発症，進展増悪と定義した．その結果，発症は患者1,000人あたり年間38.3人にみられ，進展増悪は患者1,000人あたり年間21.1人に認められた．20年前のわが国のSasakiらの報告[11]では，日本人2型糖尿病患者において，毎年1,000人あたり39.8人に網膜症が発症したことが報告されており，それにほぼ一致した発症率であった．UKPDS[12]でも，6年間で2型糖尿病患者の22%に網膜症が発生したことが報告され，年間発症率としては日本のデータに近い．

網膜症のリスクファクター

これまでの多くの研究では，糖尿病罹病期間を除くと，血糖コントロールが最も強い網膜症のリスクファクターであり，次いで血圧が有意なリスクファクターであるとされている[13]．JDCSにおける網膜症発症の有意なリスクファクターは，糖尿病罹病期間（5年あたり1.3倍），HbA1c（1%あたり1.4倍），BMI（body mass index，1 kg/m^{2}あたり1.1倍），収縮期血圧（10 mmHgあたり1.1倍）であり，進展増悪の有意なリスクファクターはHbA1c（1%あたり1.7倍）のみであった[10]．血糖コントロールが発症と進展増悪に及ぼす影響を図2に示した．その結果，開始時HbA1c 9%以上の患者では，ほぼ半数がその後8年間に網膜症を発症し，進展増悪率も非常に高いことが明らかになった．一方，HbA1c 7%未満であっても1割に網膜症の発症がみられたことから，発症予防にはかなり厳格な血糖コント

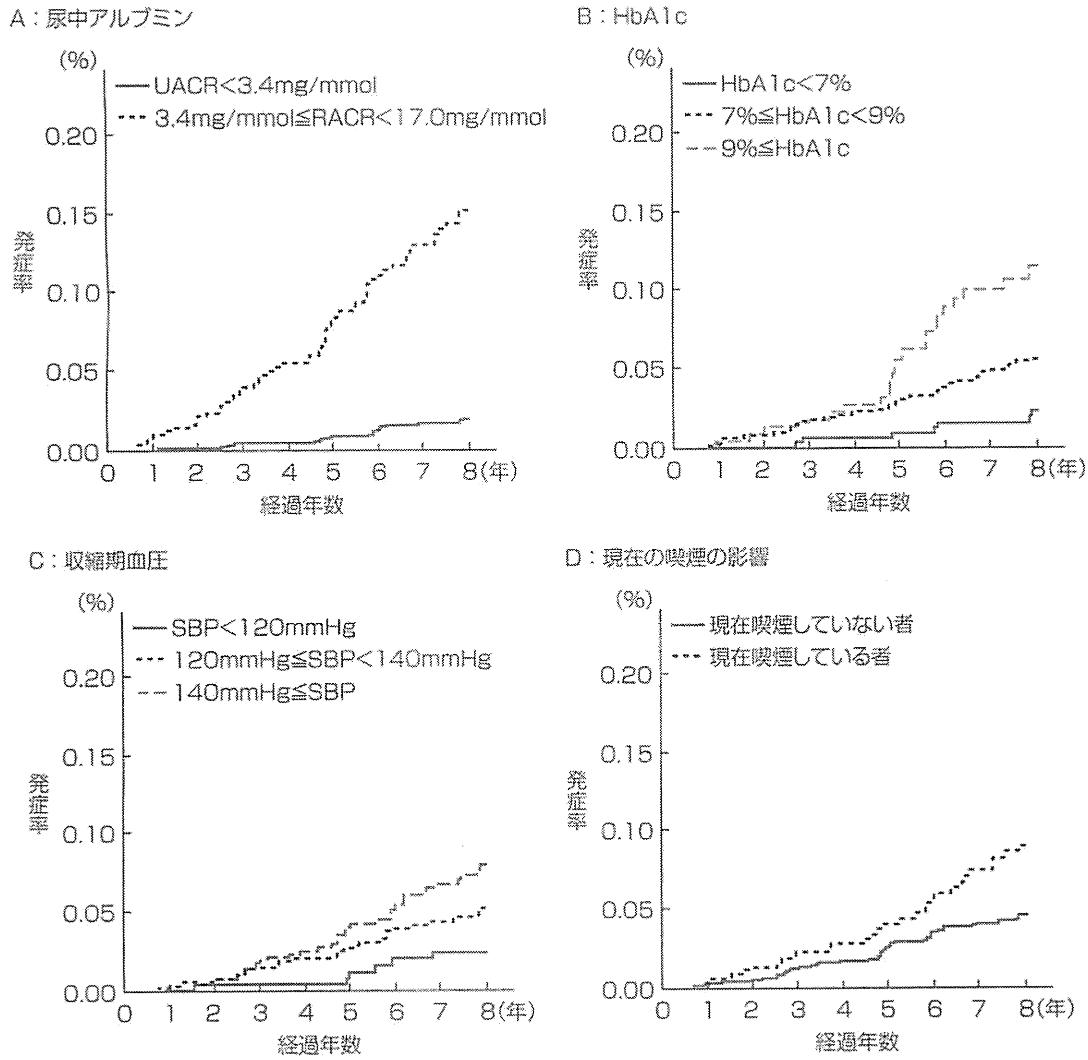

図1　JDCSにおける顕性腎症の進行に対する各種リスクファクター（Kaplan-Meier解析）
（文献2）より引用）

ロールが必要である．

神経障害について

ヨーロッパの1型糖尿病患者を対象にした研究[14]では，神経障害のリスクファクターの多くが大血管症，すなわち動脈硬化のそれと共通であった．しかしJDCSでは，肥満を除いて両者の共通性はみられず，危険因子が糖尿病の型や人種により大きく異なることが示された[15]．

大血管症の発症率と関連因子

わが国を含む東アジアでは，欧米と比較して冠動脈疾患の発症率が低いことがよく知られている．糖尿病患者でも，欧米では約8割が大血管症で死亡するのに対し[16]，わが国の糖尿病患者の筆頭死因は悪性新生物であり心血管疾患ではない[17]．一方，糖尿病患者の心血管疾患発症リスクが，非糖尿病者の2～4倍高いことについては，わが国でも欧米でも共通である．世界102件の前向き研究

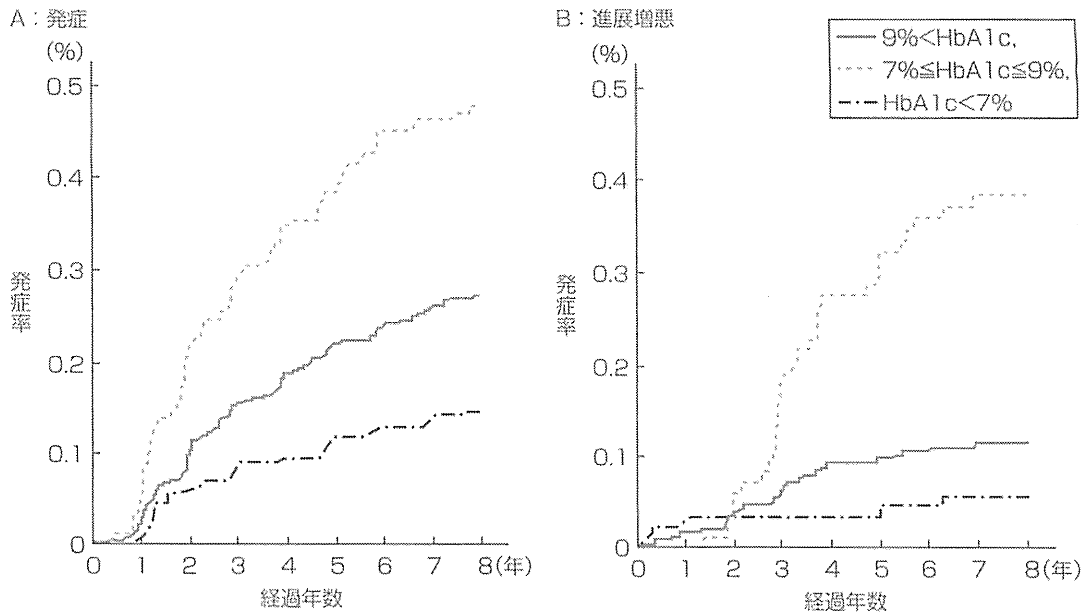

図2 JDCSにおける網膜症の発症（図1A）ならびに進展増悪（図1B）に対する開始時HbA1cの影響（Kaplan-Meier解析）
（文献10）より引用）

のメタアナリシス[18]では，糖尿病患者は，冠動脈疾患，虚血性脳梗塞の発症リスクが，非糖尿病患者のそれぞれ2.00倍（95% CI 1.83～2.19），2.27倍（95% CI 1.95～2.65）に高まる．わが国の検討[19]でも，糖尿病患者では正常耐糖能者と比較して，脳梗塞の発症が，男性で2.54倍（95% CI 1.4～4.63），女性で2.02倍（95% CI 1.07～3.81）と有意に高く，女性では冠動脈疾患が3.46倍（95% CI 1.59～7.54）と有意に増加していた．

JDCSにおける大血管症の発症率は，冠動脈疾患（狭心症と心筋梗塞）は患者1,000人あたり年間9.6（男性11.2，女性7.9）人に，脳卒中（脳梗塞，脳出血と一過性脳虚血発作〈transient ischemic attack；TIA〉）は7.5（男性8.7，女性6.1）人であった[20]．これらは一般住民[21]と比較して，冠動脈疾患で約3倍，脳卒中で約2倍高率であった（表1）．ただし，一般住民にも糖尿病・耐糖能障害者が約3割含まれているため[21]，糖尿病者の非糖尿病者に対する実際のリスクはより大きい．大血管症発症者と非発症者間で，開始時の腹囲に有意差はみられず[22]，メタボリックシンドロームの診断基準も大血管症の予測にはそれほど有用でないことが判明した[23,24]．同じことはその後，UKPDSでも確認された[25]．しかし，診断基準の一部を修飾すれば予測能が改善する可能性は残されており[26]，大血管症の高リスク者のスクリーニング法についてはさらに検討の余地が残されている．

生活習慣介入の合併症抑制効果

多くの研究により，食事療法や運動療法を中心とした生活習慣教育が，糖尿病の発症を抑制することが知られている．しかし，すでに糖尿病になった患者において，その合併症を抑制するかどうかが明らかではなかった．JDCSはこの点を明らかにするために対象患者を「従来治療群（対照群）」と「生活習慣介入群（強化治療群）」に無作為に割り付け，前者では各専門施設のそれまでの外来治療を継続し，後者ではそれに加えて，生活習慣教育

表1 日本人2型糖尿病患者，日本人一般住民ならびにイギリス人糖尿病患者の心血管疾患発症率

	冠動脈心疾患	脳卒中
日本人2型糖尿病患者（JDCS 9年次）	9.6（男11.2/女7.9）	7.5（男8.7/女6.1）
日本人一般住民（久山町研究第3集団*）	男3.5/女1.8	男5.3/女3.9
イギリス人2型糖尿病患者（UKPDS対照群）	17.4	5.0

1,000人年あたりの発症数.
*：約30%の糖尿病・耐糖能異常者を含む

を中心とした強化治療を追加した[27].

その内容は，①血糖，肥満度，血清脂質，血圧などについてガイドラインに基づくコントロール目標（表2）の設定，②その達成を目標とした，外来主治医による生活習慣指導を中心とした強化治療，③保健師など糖尿病療養指導者の，電話による定期的な生活療養指導，④コントロール目標を満たさない患者に対し，パンフレットなど教育資料の送付や，来院頻度増加や教育入院，などである．対照群をコントロール不良のまま長期にわたり放置しないという倫理的配慮に基づき，内服薬やインスリンの変更は両群ともに妨げなかったが，結果的には両群間の投薬頻度に有意差はなかった．

HbA1cは，開始2～5年目の間だけ，介入群が非介入群よりわずか（約0.2%）だが有意に低い値を示した．しかしHbA1c以外の体重，血圧，血清脂質，喫煙率などについては両群間に有意差を認めなかった．両群のコントロール指標の差が小さかった理由として，本研究が糖尿病専門施設で実施されたため，対照群患者に対する教育指導内容が元から充実しており，追加の生活習慣指導介入の効果が現れにくかったためと推測された．

8年間の追跡期間中，網膜症，腎症，冠動脈疾患の発症率については有意差がみられなかったものの，脳卒中に関しては，従来治療群の発症率9.52/1,000人年に対して，生活習慣介入群の発症率は5.48/1,000人年と有意に低く，生活習慣介入群では，脳卒中発症リスクは，従来治療群の0.62（95% CI 0.39～0.98，

表2 JDCS介入群の治療到達目標
下線は2004年修正項目

HbA1c＜6.0%
BMI＜22 kg/m^2
ウエスト/ヒップ比＜0.9（男），＜0.8（女）
血圧＜140/85 mmHg
　→130/80 mmHg
総コレステロール＜220 mg/dL
　→180 mg/dL またはLDLコレステロール＜100 mg/dL
トリグリセロール＜150 mg/dL
HDLコレステロール＞40 mg/dL
禁煙，禁酒（2単位/日未満）

p＝0.04）倍であった[27]（図3）．おもな心血管危険リスクファクターに群間有意差がなかったにもかかわらず，脳卒中発症率が介入群で有意に低かった理由として，過去にみられた血糖コントロールの“legacy effect（遺産効果）”，両群間のわずかな運動量の違いの他，生活習慣指導に伴うその他の未知の因子が関与した可能性が推測されている．わが国の高齢2型糖尿病患者において，well-beingな状態も脳卒中発症リスクと関連していたことも報告されており[28]，患者教育が精神的ストレスや不安感の低減などを通じて脳卒中抑制に寄与した可能性も考えられる．今後JDCSにより，日本人2型糖尿病患者とその血管合併症の特徴がさらに明らかにされ，日本人糖尿病患者に最適化された合併症の予防・治療法確立に貢献することが期待される．

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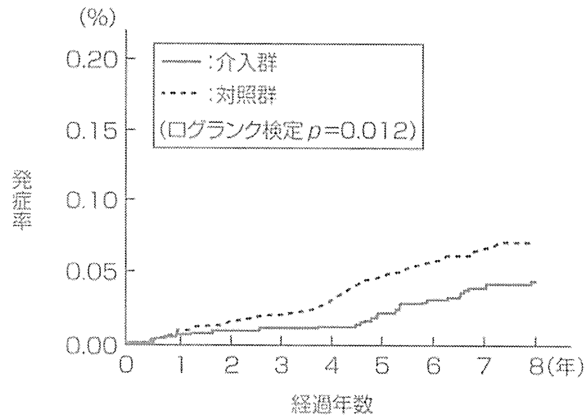

図3 JDCSにおける生活習慣介入の脳卒中発症率に対する効果(Kaplan-Meier解析)
(文献27)より)

先生らが担当されています．また本研究は，下記糖尿病専門施設の共同研究であり，ご参加いただいている多くの先生方・関係者・患者さんのご尽力に深謝いたします．

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第52回日本老年医学会学術集会記録
〈シンポジウム2：動脈硬化の予防と治療〉

4. 動脈硬化の予防と治療—糖尿病

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Key words：糖尿病大血管合併症，血糖コントロール，血圧コントロール，脂質コントロール，生活習慣介入
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糖尿病と動脈硬化

日本は，40歳以上の3人に1人が，糖尿病またはその疑いが強い「糖尿病大国」である．糖尿病の血管合併症には，糖尿病特異的な細小血管合併症と，糖尿病特異的でない冠動脈疾患や脳卒中などの動脈硬化性合併症があり，後者を大血管合併症ともいう．大血管合併症は糖尿病患者の生命予後に直結し，細小血管合併症がまだ見られないような初期から発症し始める．

糖尿病では，高血糖とインスリン感受性低下（インスリン抵抗性）を背景とし，タンパクの糖化や酸化ストレスの亢進，血管内皮機能障害，各種リポタンパク異常（酸化LDLやsmall dense LDL，レムナントリポタンパクの産生増加）など多くの動脈硬化促進メカニズムが多発する．その結果，糖尿病患者は非糖尿病者と比較して数倍以上動脈硬化疾患を発症しやすい．

冠動脈疾患患者は，再度冠動脈疾患を起こしやすいが，糖尿病患者では冠動脈疾患の既往がなくても，冠動脈疾患既往のある非糖尿病者と同じくらい冠動脈疾患のリスクが高い[1]．糖尿病患者の冠動脈疾患の起こりやすさは，非糖尿病者と比較した場合，年齢換算で15歳分にもなる[1]．わが国でも，糖尿病未診断の急性冠動脈症候群患者に経口糖負荷試験を行うと，半数近くに糖尿病や耐糖能障害がみつかる[2]．したがって糖尿病に気づかずに，動脈硬化合併症を発症する例は非常に多い．

糖尿病患者における動脈硬化疾患の発症率

欧米では糖尿病患者の8割が大血管合併症で死亡する．これに対し日本を含む東アジア地域では，冠動脈疾患発症率が欧米より低いことが特徴とされてきた．しかし日本人糖尿病患者においても，従来多かった腎疾患による死亡が減少し，相対的に冠動脈疾患による死亡が増えつつある．

Japan Diabetes Complications Study（JDCS）は，大学病院や大病院など全国59カ所に通院する2型糖尿病患者2,033名を対象に1996年から行われている大規模前向き研究である[3]．JDCSでは，冠動脈疾患（狭心症と心筋梗塞）の年間発症率は患者1,000人あたり9.6人，脳卒中（多くは脳梗塞）は同7.6人であった（表1）．これらは一般住民[4]の2倍以上の頻度で，一般住民にも糖尿病や耐糖能障害者が約3割含まれるため[4]，糖尿病患者と非糖尿病者との差はさらに大きい．さらに糖尿病患者では一般住民とは逆に，冠動脈疾患の頻度の方が脳卒中より高い．ただし英国人2型糖尿病患者[5]と比較すると，日本人患者の冠動脈疾患発症率はまだ低い（表1）．

血糖コントロールと動脈硬化疾患

欧米のメタアナリシス[6]によると，2型糖尿病患者のHbA1cが1%上昇すると，冠動脈疾患や脳卒中の発症リスクは約1.1～1.2倍有意に上昇する．1型糖尿病患者を対象にした米国のDiabetes Control and Complications Trial（DCCT）[7]では，強化治療群に対して平均6.6年間の血糖コントロール強化療法を実施し，その終了後も続けて従来治療群と比較したところ，介入終了後にはHbA1cの群間差が消失したにも関わらず，介入中にはみられなかった動脈硬化合併症の群間差が有意になり，その有意差は介入開始17年後でも持続していた．2型糖尿病を対象にしたUnited Kingdom Prospective Diabetes Study（UKPDS）でも同様に，血糖コントロール強化治療の心筋梗塞ならびに全原因死亡率に対する有効性が，血糖コントロールに対する強化療法終了後に出現し，その後長期にわたり継続していた[8]．このように，

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