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Projected number of diabetic renal disease patients among insulin-dependent diabetes mellitus children in Japan using a Markov model with probabilistic sensitivity analysis

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Background	To plan prevention programmes for the diabetic renal disease among insulin-dependent diabetes mellitus (IDDM) children, projections of future trends for the disease is crucial. We projected future trends in the number of diabetic renal disease patients among IDDM children and assessed an impact of treatment dissemination in Japan.
Methods	We used a Markov model to describe the clinical courses of diabetic renal disease. Future trends in the number of patients with diabetic nephropathy (DN) and end-stage renal disease (ESRD) were projected from the year 1995 to 2015. We made three scenarios for assessing an impact of the dissemination of new treatment. We performed a probabilistic sensitivity analysis for the uncertainty of transition probabilities.
Results	The results showed that the number of patients with DN was 790.5 (5th to 95th percentile: 652.5–955.1), ESRD was 253.3 (5th to 95th percentile: 207.3–310.0) in year 2015 on basic scenario. Considering the dissemination of intensive insulin therapy, under the scenario of the gradual increase of the treatment, the result showed that the number of patients with DN was 713.1 (5th to 95th percentile: 546.2–930.6), ESRD was 231.0 (5th to 95th percentile: 176.6–296.2). Under the scenario of the immediate change of the treatment, the results showed that the number of patients with DN in 2015 was 418.9 (5th percentile; 345.4; 95th percentile; 506.1) and with ESRD was 133.4 (5th percentile; 109.0; 95th percentile; 163.8).
Conclusions	The results of the projection showed a gradual increase in the number of patients with DMN and ESRD. Examination of three possible scenarios showed that the programme of dissemination of intensive insulin therapy prevented the progression of diabetic renal disease.

Keywords	Insulin-dependent diabetes mellitus, diabetic nephropathy, end-stage renal disease, Markov model, probabilistic sensitivity analysis, projection
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Diabetic renal disease (diabetic nephropathy and end-stage renal disease) is one of the severe complications among cases of juvenile-onset insulin-dependent diabetes mellitus (IDDM). A number of IDDM children develop diabetic nephropathy (DN) and progress to end-stage renal disease (ESRD). The physical and economic burdens of this disease (e.g. renal dialysis) must be borne by patients for a long time, and their quality of life continues to diminish with the progression of the disease. Thus it is important for the health planner to develop an effective prevention programme for the progression of diabetic renal disease. To do so, one must project the future trend of the disease. Moreover, it is important to evaluate the impact of the prevention programme using a projection model. The linear regression method is a popular approach to project future trends in the number of patients. Ruwaad *et al*. projected the

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Table 1 Data sources used in this study (Figure 1)

Measures	Disease state		Type of study	Reference
Annual incidence rate	IDDM[a]	λ_1	Epidemiological	10
	DN[b] in IDDM patients	λ_2	Hospital-based	11
	ESRD[c] in DN patients	λ_3	Hospital-based (in US)	12
Annual mortality rate	non-IDDM	μ_1	Vital statistics	9
	IDDM	μ_2	Epidemiological	13
	DN	μ_3	Published reports + vital statistics	9,14
	ESRD	μ_4	Epidemiological	15

[a] Insulin-dependent diabetes mellitus.

[b] Diabetic nephropathy.

[c] End-stage renal disease.

number of diabetic patients in The Netherlands using the linear regression approach.[1] Green *et al*. showed the future trends of the number of patients with IDDM in a county of Denmark by a simple mathematical model.[2] In Japan, Nakamura *et al*. estimated the number of patients with diabetes mellitus by linear regression based on the results of National Patient Surveys.[3] Projection with a linear regression is easy to calculate and the results may be valid for a short-term projection. However, the regression approach does not reflect the clinical course of the disease in the model, and does not easily account for future changes in treatment. The projection using a Markov model is another projection method that can easily reflect the clinical course of the disease.[4,5] It has been widely used in the field of medical decision making, and several applications for IDDM and diabetic renal disease are found in the literature.[6,7] In a projection using the Markov model, many transition probabilities are sometimes uncertain because of bias and sampling variation. Consideration of this problem is needed in order to make a projection using a Markov model. Probabilistic sensitivity analysis,[8] in which uncertainties of transition probabilities may be considered simultaneously, is one way to overcome the problems with projections using the Markov model.

In the present study, we developed several scenarios and projected the trends for 20 years in the number of diabetic renal disease (DN, ESRD) patients among IDDM children aged 0–18 in year 1995. We also estimated the range of this projected number of patients by using probabilistic sensitivity analysis.

Methods

Data sources

The data used in this study are listed in Table 1. Most of the data were collected from major epidemiological studies of IDDM and its complications published in Japan. Numbers of children born in 1977–1994, the initial cohort of projection, were collected from the vital statistics in Japan.[9] The age-specific incidence rates of IDDM in three areas in Japan were shown in Table 2. These data were obtained from epidemiological studies of IDDM children in Japan.[10] To summarize the data, we made a weighted average of these incidence rates, whose weights were the inverse of the variance. For the incidence rate of DN in the IDDM population, we referred to a hospital-based study conducted in Japan.[11] These data, which included the age-specific, IDDM-duration specific incidence rates, were shown in Table 3. There are no published data on the incidence rate of ESRD among patients with DN in Japan, so we used the incidence rate in the United States.[12]

The mortality rate of non-IDDM used was from the vital statistics.[9] The IDDM mortality rate was derived from data in the published literature.[13] To estimate the DN mortality rate, we used a risk ratio (mortality from DN)/(mortality from IDDM), from a published report [14] and multiplied the risk ratio by the mortality in IDDM cases. The ESRD mortality rate used was also from a published study.[15]

Markov model and projections

To project the future number of patients with DN and ESRD, we modelled a clinical course of diabetic renal disease in IDDM. The proposed Markov model for the clinical course was shown in Figure 1. This model was based on previous models,[16–18] and consisted of five mutually exclusive states (non-IDDM, IDDM, DN, ESRD, death). All 12 arrows in the model indicate the progression of the diabetic renal diseases. In accordance with various studies,[16–18] we assumed the disease processes were progressive and there was no regression from a present state to a previous one. To calculate the projected number of patients, we made the matrices to express the progression of the disease states using the Markov model.[19,20] This calculation process represents a standard implementation of a non-stationary Markov process. A Markov model was run independently for each age of diabetes onset. The model was implemented by creating matrices for the transition probabilities from one disease state to the next during a one-year period. The above expression was written in a matrix form:

$$Y_{i(t+1)} = M_{it} Y_{it}$$

Table 2 Age-specific annual incidence rates of IDDM in Japan

Region	Age group (years)	Incidence rate ($\times 10^{-6}$)	95% CI
Hokkaido (Northern Japan)	0–4	0.74	0.39–1.26
	5–9	1.43	0.96–2.06
	10–14	3.65	3.29–4.56
Tokyo (Central Japan)	0–4	1.16	0.72–1.78
	5–9	1.68	1.14–2.37
	10–14	2.01	1.46–2.67
Kagoshima (Southern Japan)	0–4	1.48	0.88–2.33
	5–9	1.76	1.11–2.63
	10–14	2.07	1.39–2.98
Weighted average of three areas	0–4	1.13	1.11–1.16
	5–9	1.61	1.59–1.63
	10–14	3.02	3.01–3.04

Table 3 Annal incidence rates of diabetic renal disease

Disease state	Onset age group of IDDM[a]	Duration of IDDM (year)	Incidence rate	Limit of uncertainty	
				low	high
non-IDDM to IDDM	0–4		1.13×10^{-6}	0.11×10^{-6}	3.62×10^{-6}
	5–9		1.61×10^{-6}	1.16×10^{-6}	5.17×10^{-6}
	10–14		3.02×10^{-6}	0.30×10^{-6}	9.81×10^{-6}
IDDM to DN[b]	0–8	0–10	0.001	0.0001	0.0035
		11–15	0.017	0.0017	0.0669
		16–20	0.018	0.0018	0.0709
		21–25	0.010	0.0010	0.0385
		26–30	0.000	0.0000	0.0000
	9–17	0–10	0.001	0.0001	0.0035
		11–15	0.035	0.0035	0.1400
		16–20	0.042	0.0042	0.1680
		21–25	0.009	0.0009	0.0345
		26–30	0.000	0.0000	0.0000
	18–29	0–10	0.003	0.0003	0.0110
		11–15	0.031	0.0031	0.1239
		16–20	0.042	0.0042	0.1680
		21–25	0.042	0.0042	0.1680
		26–30	0.054	0.0054	0.2149
DN to ESRD[c]			0.068	0.0068	0.2675

[a] Insulin-dependent diabetes mellitus.

[b] Diabetic nephropathy.

[c] End-stage renal disease.

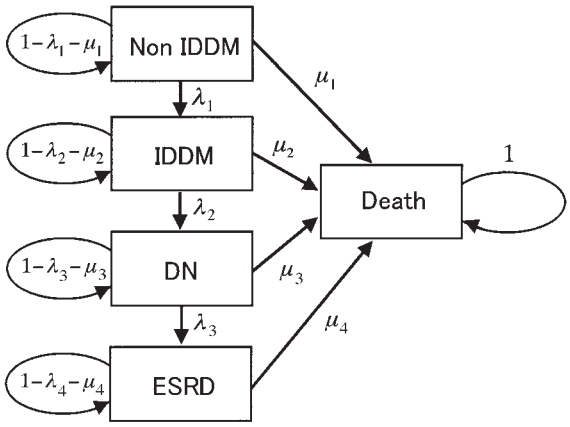

Figure 1 Flow charts for the development of diabetic renal disease

Each arrow represents the progression of a disease state.
IDDM: Insulin-dependent diabetes mellitus.
DN: Diabetic nephropathy.
ESRD: End-stage renal disease.
λ_1: Transition probability from non-IDDM to IDDM.
λ_2: Transition probability from IDDM to DN.
λ_3: Transition probability from DN to ESRD.
μ_1: Mortality rate of non-IDDM.
μ_2: Mortality rate of IDDM.
μ_3: Mortality rate of DN.
μ_4: Mortality rate of ESRD.

where i is a disease state (i = 1: non-IDDM; 2: IDDM; 3: DN; 4: ESRD; 5: Death), t is age, M_{it} is a matrix of transition probabilities of disease state i, age t, and Y_{it} is a vector that represents a number of patients with each disease state.

To assess the impact of dissemination of intensive insulin therapy (an effective treatment for IDDM). We created three scenarios for future changes in IDDM treatment: In scenario 1, dissemination of the intensive insulin therapy remains at the level it was in 1995; in scenario 2, its dissemination increases linearly so as to reach 100% in 2015; and in scenario 3, it reaches 100% in 1995. To reflect the influence of the dissemination of a new treatment in scenario 2, we made an equation;

$$\lambda_x = \lambda_{1995} + \frac{(\lambda_{1995} - \lambda_{2015})}{20} (x - 1995)$$

where λ_x is the incidence rate of DN in year x, λ_{1995} is the incidence rate of DN in 1995, and λ_{2015} is the incidence rate of DN in 2015.

λ_{1995} and λ_{2015} were estimated;

$$\lambda_{1995} = (0.6 \times 0.49 + 0.4) \times \lambda_{DN}$$

$$\lambda_{2015} = 0.49\lambda_{DN}$$

where λ_{DN} is the incidence rate of DN in Japan.

We assumed that the diffusion of the intensive insulin therapy in Japan was 0.6, which was based on a report. The above formula represented a weighted average of 0.49 λ_{DN} (the incidence rate of intensive insulin therapy) and λ_{DN} (the incidence rate of conventional insulin therapy). The value 0.49 represented the incidence rate ratio of the Diabetes Control and Complications Trial (DCCT).[21]

Uncertainty of transition probabilities

To assess the uncertainty of transition probabilities (e.g. annual incidence rate, annual mortality rate), we used the probabilistic sensitivity analysis proposed by Doubilet *et al.*[8]—a method for determining the distribution of transition probabilities in a Markov model. In the analysis, we used Monte Carlo simulation instead of precise calculation of the distribution of the number of patients. In this simulation, each transition probability was randomly assigned a value from its distribution, and the number of patients was computed in each process. This process was repeated many times, and we finally determined the distribution of the number of patients. The procedure used to specify the parameters of the sampling distribution, proposed by Doubilet *et al*.[8] To decide the form of the sampling distribution, we used the transition probabilities and 10% of the transition probabilities for the mean of the required distribution and the lower bound of uncertainty, respectively. The distribution of the number of patients was estimated from the outputs of 1000 model runs using Monte Carlo simulation. All analyses were performed by SAS release 6.12.[22]

Comparison with published data

To estimate future trends for 20 years in patients with DN and ESRD among the IDDM children aged 0–18 in 1995, we used the birth cohort (1974–1995) to project the number of IDDM children aged 0–18 in 1995 by the Markov model. To validate the results of the projection, we compared them with the two sets of data in Japan. One set was the prevalence of diabetes mellitus, which includes the prevalence of IDDM children.[23] By multiplying the prevalence of IDDM by the demographic data in year 1995 from the vital statistics in Japan, we estimated the number of IDDM patients aged 0–18 in 1995. The other set of data was the number of juvenile-onset diabetes mellitus patients receiving government support through the medical benefit system in Japan.[24] The data included the number of patients with two types of diabetes mellitus, non-insulin dependent diabetes mellitus and insulin-dependent diabetes mellitus (or IDDM). To estimate the number of IDDM children from the data, we calculated the number of juvenile-onset diabetes mellitus patients multiplied by the proportion of IDDM among such cases. This proportion was derived from the survey data.[25]

Results

Figure 2 shows the distribution in the projected number of IDDM children aged 0–18 in 1995. To take into account the uncertainty of the transition probabilities, the projected numbers of patients were shown in the distribution form. The mean of the distribution was 3819.5 (5th percentile: 3214.9, 95th percentile: 4551.7). By using the reported IDDM prevalence, the estimated number of IDDM children aged 0–18 in year 1995 was 2621.7. By using the number of cases of juvenile-onset diabetes mellitus receiving medical benefits from the government in Japan, the estimated number of IDDM children aged 0–18 in 1995 was found to be 5161.6. The projected number of patients with IDDM that year ranged between the two estimates for the number of IDDM children.

Future trends in the projected number of patients with diabetic renal disease until 2015 were presented in Figure 3 according to the above-mentioned three scenarios. The results

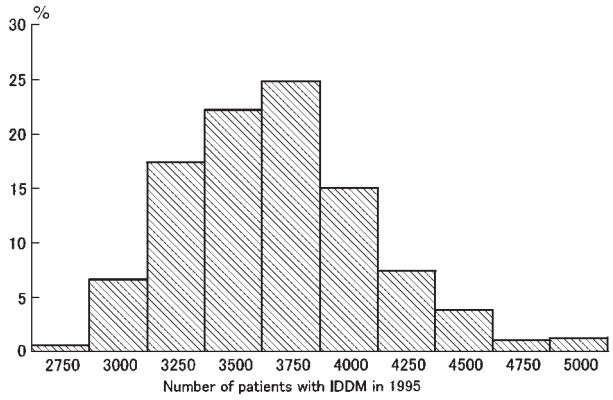

Figure 2 Distribution of the projected number of IDDM patients in 1995

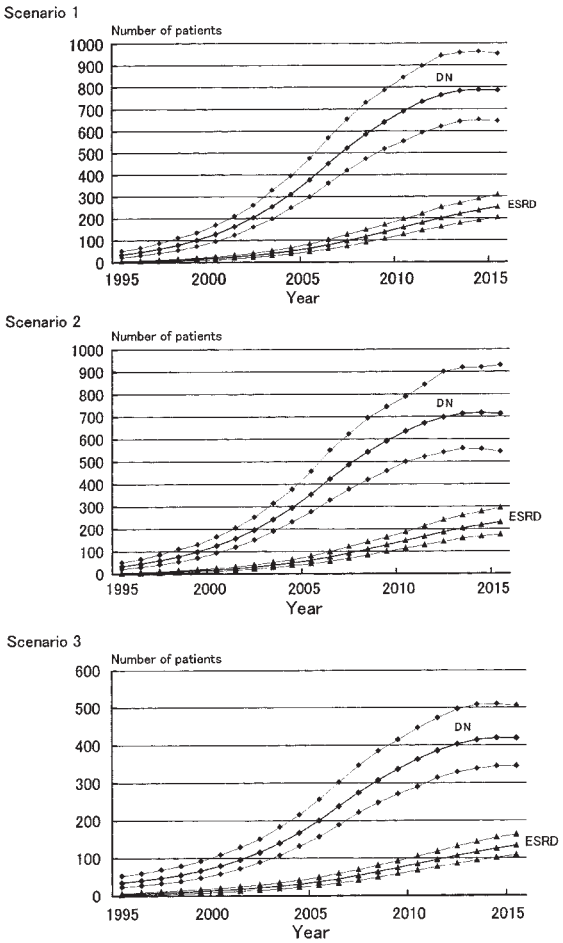

Figure 3 Projection of the number of diabetic renal disease in IDDM children aged 1–18 in year 1995

Straight lines represent the average number of patients.
Broken lines represent 5 percentile and 95 percentile of the number of patients.
DN: Diabetic nephropathy.
ESRD: End-stage renal disease.

Table 4 The projected number of patients with diabetic renal disease in 2015

	DN[a]	ESRD[b]
Scenario 1	790.5 (652.5, 955.1)	253.3 (207.3, 310.0)
Scenario 2	713.1 (546.2, 930.6)	231.0 (176.6, 296.2)
Scenario 3	418.9 (345.4, 506.1)	133.4 (109.0, 163.8)

A number of 5th percentile and 95th percentile were represented within the parentheses.

[a] Diabetic nephropathy.

[b] End-stage renal disease.

showed there was a gradual increase in the number of patients with DN and ESRD. Table 4 summarized the projected numbers of DN and ESRD patients in 2015. The number of patients with DN projected for that year is 790.5 (5th percentile: 652.5; 95th percentile: 955.1) in scenario 1, 713.1 (5th percentile: 546.2; 95th percentile: 930.6) in scenario 2, and 418.9 (5th percentile: 345.4; 95th percentile: 506.1) in scenario 3. The number of patients with ESRD projected for 2015 is 253.3 (5th percentile: 207.3; 95th percentile: 310.0) in scenario 1, 231.0 (5th percentile: 176.6; 95th percentile: 296.2) in scenario 2, and 133.4 (5th percentile: 109.0; 95th percentile: 163.8) in scenario 3.

Discussion

The projection of future trends is important for public health professionals who plan to improve health status in Japan. Our results showed that there was a gradual increase in the number of patients with DN and ESRD. Our results also showed an impact of the new treatment, intensive insulin therapy by comparing the results of projections under three scenarios. The results of the reduction in number of patients implied that the dissemination of the new treatment would be necessary for public health perspectives.

The diagram of Markov model used for expressing a clinical course of IDDM came from the results of clinical research. Data we used for the projection were all collected from the published epidemiological papers and demographic data. Integrating the diagram of clinical research and data from epidemiological study made our projections possible. This was a good illustration of how distinct sources of epidemiological data can be combined by a means useful to health care professionals.

There were several limitations to this study. The first issue is the validity of transition probabilities used in this projection. In Japan, there were few epidemiological studies in the IDDM population and age-specific, IDDM duration-specific transition probabilities were seldom available. In the selection of epidemiological data, we chose the study of incidence (not prevalence) data with a large sample size. The transition probabilities were representative figures from the Japanese population. If no data were available for Japan, we substituted the transition probabilities from other countries. The transition probability from DN to ESRD was substituted by published data from the Josulin clinic in the USA. The problem of inadequate data for projection would be overcome by the accumulation of research results in future.

The second issue is the method for sensitivity analysis to consider the uncertainty of transition probabilities. We adopted probabilistic sensitivity analysis to consider the uncertainty of the transition probabilities. The advantages of probabilistic sensitivity analysis over n-way sensitivity analysis are that one can handle the uncertainty of many transition probabilities together, and describe the result of the projection in a distribution form. When extremely high transition probabilities were simultaneously selected in the simulation, n-way sensitivity analysis showed an unrealistically high number of patients. Meanwhile, in the probabilistic sensitivity analysis, an impossibly high number of patients were found with low probability. We specified that the transition probability had a logistic-normal distribution, an option we had chosen for the sampling distribution; it was possible to choose other types of distribution in the probabilistic sensitivity analysis. The reasons for selecting the logistic-normal distribution for the sampling distribution were the following: (1) The logistic-normal distribution is a right-tailed distribution. Most of the transition probabilities were close to zero, and a right-tailed distribution was suitable for a sampling distribution of transition probabilities. (2) The form of the logistic-normal distribution was determined by the mean and lower boundary of uncertainty only. In the projection using the Markov model, there was no information on the actual distribution of the transition probability, so specification of the shape of logistic-normal distribution was more practical.

The final issue is the assumption of the three scenarios in this study. We made three scenarios to assess the impact of the dissemination of intensive insulin therapy. In fact, the dissemination rate of intensive insulin therapy is gradually increasing in Japan. From a projection viewpoint, scenario 1 and scenario 3 are hypothetical examples and the expected number of the patients is between the projected numbers of these two scenarios. So the projected number of patients from scenario 2 is more realistic than that of the other two. From an evaluation viewpoint which assesses the impact of a health programme by Markov model simulation, scenario 1 means no health programme and scenario 3 means an extensive health programme. By comparing these two extreme cases, the impact of the dissemination of new treatment might be clarified and the efficacy of the health programme might be fully described

In conclusion, we projected future trends over 20 years in the number of patients with diabetic renal disease (DN, ESRD) in IDDM children aged 0–18 in 1995. We also projected the range of the projected number using probabilistic sensitivity analysis. The results showed a gradual increase in the number of patients with DN and ESRD. By comparing the results of three projections, we showed that the dissemination of intensive insulin therapy prevented progression of diabetic renal disease.

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