Specific immunotherapy and asthma control

Imunoterapia específica e controlo da asma

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ABSTRACT

Background: Specific immunotherapy (SIT) is associated with immunological modulation and is therefore able to induce progressive and sustained clinical improvements in allergic asthmatic patients. **Aim:** To assess SIT efficacy in maintaining asthma control. **Material and Methods:** In March 2007 a clinical questionnaire and the Asthma Control Test (ACT) were filled in by 252 asthmatic patients during their specialist hospital appointment and in the presence of their allergologist. In March 2010 we sent the ACT and a new clinical questionnaire by mail to the same 252 patients. We compared their answers and ACT scores from 2007 to 2010 and between patients who had received SIT and those who hadn't. **Results:** We obtained 96 answers, 29 from asthmatics who had received at least 4 years of SIT and 67 from non--SIT-treated asthmatics. Both groups of patients had a slightly lower mean ACT score in 2010 than 2007 (22.2 *vs.* 22.7 in SIT-treated and 20.9 *vs.* 21.2 in non-SIT-treated patients) but without significant differences. However, in 2010 only 30% of SIT-treated patients were using daily inhaled steroids versus 62% of the non-SIT-treated patients ($p<0.01$). Equally so, systemic steroids were used in 17% of the non-SIT-treated patients and in 0% of the SIT-treated ($p=0.03$). SIT-treated patients had also lesser recourse to A&E (1.5 *vs.* 3.2; $p=0.02$) and a lower rate of self-reported diabetes (0 *vs.* 10%; $p=0.03$). Although asthma control was generally good, we highlight the fact that around 30% of patients in both groups experienced some limitations to their daily lives due to their asthma. **Conclusions:** Most patients under specialised allergology follow-up maintained good levels of asthma control over 3 years. In the SIT-treated patients we observed additional improvements in other parameters, reflecting SIT's significant immune-modulating actions.

Keywords: ACT questionnaire, asthma, control, specific immunotherapy.

RESUMO

Fundamentos: *A imunoterapia específica (ITE) associa-se a uma modulação imunológica, podendo permitir, nos asmáticos alérgicos, melhorias clínicas progressivas e mantidas.* ***Objectivo:*** *Avaliar os efeitos da ITE na manutenção do controlo da asma.* ***Material e métodos:*** *Em Março/2007 foi preenchido, na presença do alergologista assistente, um questionário clínico e o* Asthma Control Test *(ACT) por 252 doentes asmáticos, já seguidos em consulta hospitalar de Alergologia. Em Março/2010 enviámos pelo correio aos 252 doentes um novo questionário clínico e o ACT, comparando-se as respostas entre os doentes tratados com ITE+farmacoterapia e os que receberam apenas farmacoterapia.* ***Resultados:*** *Obtivemos 96 respostas, 29 das quais de asmáticos que tinham recebido pelo menos quatro anos de ITE e 67 sem ITE. Os dois grupos de doentes apresentavam em 2010 uma média de pontuações ACT ligeiramente inferior a 2007 (22,2 versus 22,7 no grupo sob ITE e 20,9* versus *21,2 no grupo sem ITE), mas sem diferenças significativas. Contudo, em 2010, apenas 30% dos doentes que receberam ITE referiram utilizar corticoterapia inalada diária, contra 62% do grupo sem ITE (p<0,01). De forma semelhante, a utilização de corticosteróides sistémicos não ocorreu em nenhum doente do grupo ITE, contra 17% do grupo sem ITE (p=0,03). No grupo ITE também se registou um menor número de idas ao serviço de urgência (1,5 vs. 3,2; p=0,02) e uma menor frequência de diabetes auto-reportada (0 vs. 10%; p=0,03). Apesar de haver um bom nível de controlo da asma em ambos os grupos, salienta-se que cerca de 30% dos doentes dos dois grupos refere algumas limitações à sua vida diária por causa da asma.* ***Conclusões:*** *A maior parte dos doentes sob seguimento especializado mantém, em três anos, bons níveis de controlo da asma. No grupo sob ITE há melhorias adicionais de outros parâmetros, reflectindo a relevante acção imunomoduladora da ITE.*

Palavras-chave: *Asma, controlo, imunoterapia específica, questionário ACT.*

INTRODUCTION

Bronchial asthma is a continuing public health problem due to its high rate and the toll it takes, particularly the non-controlled forms. This is an added burden on national health systems[1], demanding approaches which allow for a reduction in the heavy direct and indirect costs associated with this pathology. It is further stressed that despite the availability of several effective asthma-control drugs, there is a very high proportion (approx. 50-60%) of asthma patients with non-controlled asthma, as shown by different types of evaluation and in different countries[2,3].

It is known that poor control of asthma is associated with a very high risk of severe crises which need recourse to accident and emergency (A&E) services or hospital admission[4,5]. Optimising pharmacological treatment allows in many cases a high percent of patients with controlled disease, as proven by the results gleaned in Portugal from the asthma control tests administered to patients attending specialised hospital appointments[6,7] as opposed to those from the same tests given to a general population of asthmatics[8].

These results are similar to those seen in other international studies[9-11] which show a better control in patients who are under specialist care, many times due to an aggressive anti-inflammatory treatment started early.The low compliance with treatment, however, in particular with inhaled corticosteroids, and difficulties associated with the correct use of inhaler devices make it vital to implement other alternative treatments for allergic asthma. These include avoidance of the trigger allergen and specific immunotherapy (SIT), which can complement and/or replace

pharmacotherapy, always aiming to maximise control of asthma.

In addition, there is a growing raft of evidence that corticosteroids do not affect the natural course of asthma[12-14], unlike SIT, a treatment choice which attempts to modify the organism's immunological response, and whose benefits remain after treatment ends[15-17].

SIT is a treatment able to modify individual specific immunoreactivity to the allergen(s) inducing asthma and/or rhinitis. SIT's efficacy in asthma has been amply shown in clinical trials and meta-analyses[15-17]. It has also been shown to have an additional action on inhaled corticosteroid treatment[18], providing a good reason for the clinical practice of associating avoidance of the trigger allergen, pharmacotherapy and SIT in patients with allergic asthma and/or rhinitis.

Thus the aim of our study was to assess up to what advantage asthma patients who had undergone a minimum of 4 consecutive years of SIT in addition to allergologist-directed pharmacotherapy had in terms of maintained control of asthma, particularly in relation to the use of inhaled corticosteroids. A secondary aim was to evaluate if patients who had undergone SIT had less recourse to A&E due to asthma, a lesser use of systemic corticosteroids and less appearance of comorbidities such as weight gain, high blood pressure or diabetes.

MATERIAL AND METHODS

The 2007 results were gleaned using a questionnaire, as described earlier[6]. A new clinical questionnaire (Annex 1) and the Asthma Control Test (ACT®) questionnaire was posted in 2010 to the 252 asthmatic patients who had taken part in the 2007 study. The clinical questionnaire dealt with the following: trips to A&E or hospital admission for asthma, absenteeism from work, limitations to daily activities due to asthma, daily treatment for asthma, namely the use of inhaled corticosteroids, recourse to rescue medication, namely systemic corticosteroids, current weight, any high blood pressure or diabetes and need for treatment for these pathologies.

The 2007 and the 2010 answers to questions about weight, the ACT scores and the questions dealing with asthma treatment were compared in the patients who had undergone SIT and those who had not.

Statistical analysis

We used descriptive statistical measures – mean, standard deviation, median and 95% confidence interval – to describe the continuous variables. For the variable categories we described the respective frequencies and/or percentages.

For comparison of categorical and numerical variables we used Mann-Whitney tests to compare with the ACT score and age (bearing in mind the non-normal distribution) and the Student t test to compare with the body mass index (BMI) numerical variables.

We used the paired Student t test to compare the values of the numerical variables in the same students 2007-2010.

We used the chi-square test (χ^2) to compare between proportions. We considered a value of $p<0.05$ as significant.

RESULTS

In this study we obtained valid completed questionnaires for 96 patients, a response rate of 38% for the 252 questionnaires sent out. Around 30.2% (29 patients)

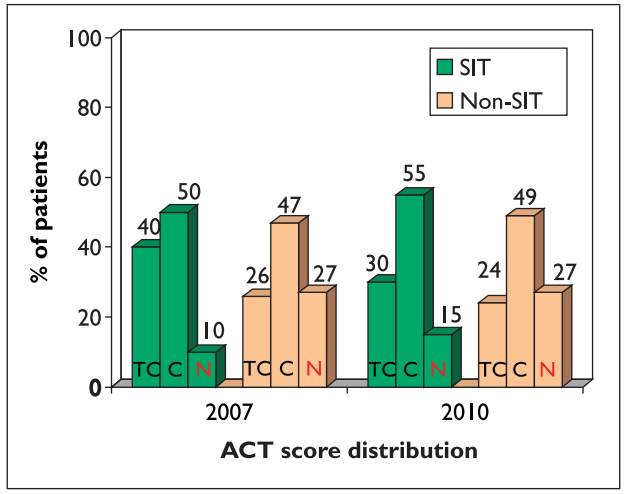
Table I. Demographic data on the two asthmatic populations

	252 asthmatics in 2007 (reference 6)		96 asthmatics in 2010 (this study)	
	Drugs + SIT (n=59)	**Drugs (n=193)**	**Drugs + SIT (n=29)**	**Drugs (n=67)**
% of females	56	63	75	67
% of atopics	100	75	100	74
Mean (SD) age in 2007 (years)	33 (13,6)	43 (18,7)	34 (13,0)	47 (16,7)
% PEFR<60% in 2007	2	16	3	15
% PEFR<80% in 2007	29	45	31	46
% global SIT	23,6		30,2	

SD – standard deviation; PEFR – peak expiratory flow rate; SIT – specific immunotherapy

of those who responded had undergone at least four years of SIT, a slightly higher proportion than those polled in 2007, when only 23.6% of patients were undergoing SIT. The remaining 67 patients had not undergone SIT. Table I shows the demographic breakdown of the population of patients interviewed in 2007 and 2010. There were no significant differences seen in the populations of asthma patients in 2010 and 2007. We foreground, however, a significantly lower mean age in the asthma patients who had undergone SIT, just as was seen in the 2007 study[6].

Figure 1 and Table II shows the comparative evaluation of the scores gleaned in the ACT questionnaires 2007 and 2010. Both groups had a slight drop in mean ACT values (-0.28 in the non-SIT group and -0.55 in the SIT group), with no statistically significant difference in the variation seen in the global population or in either group. The mean ACT scores of patients with SIT were higher than those of patients under pharmacotherapy only in both evaluations (22.7 *vs.* 21.2 in 2007 and 22.2 vs. 20.9 in 2010). These differences did not attain statistical significance, however.



TC – total control (ACT=25); C – control (ACT 20-24); N – not controlled (ACT < 20); ACT – Asthma Control Test; SIT – specific immunotherapy

Figure 1. ACT scores in 2007 and 2010 (67 SIT patients and 29 non-SIT patients)

Table III shows the percentages of patients in each group who maintained or changed ACT class, among the three possible classifications. It was seen that in both groups and in the greater part of cases, this classification

Table II. Description of the ACT scores in the SIT and non-SIT patients

	67 asthmatics on pharmacotherapy		29 asthmatics on pharmacotherapy + SIT	
	2007	**2010**	**2007**	**2010**
Mean	21,2	20,9	22,7	22,2
Standard-deviation	4,2	4,3	3,2	3,6
Median	23	23	23	24
Confidence interval of 95%	20,1 - 22,3	19,8 - 22,0	21,3 - 24,1	20,7 - 23,6

ACT – Asthma Control Test; SIT – specific immunotherapy

Table III. Variations 2007–2010 in the ACT classifications in the SIT and non-SIT patients

67 asthmatics on pharmacotherapy				29 patients on pharmacotherapy + SIT			
2010 / 2007	**% ACT 25 (n=17)**	**% ACT 20-24 (n=32)**	**% ACT <20 (n=18)**	2010 / 2007	**% ACT 25 (n=11)**	**% ACT 20-24 (n=14)**	**% ACT <20 (n=4)**
%ACT 25 (n=18)	67	28	5	**%ACT 25 (n=12)**	58	42	0
%ACT 20-24 (n=30)	17	63	20	**%ACT 20-24 (n=14)**	28	58	14
%ACT <20 (n=19)	0	42	58	**%ACT <20 (n=3)**	0	33	67

ACT – Asthma Control Test; SIT – specific immunotherapy

is overall maintained at both timepoints evaluated, separated by a three-year interval. Analysing the number of patients who moved from controlled (ACT≥20) to non-controlled asthma (ACT<20) shows a lower than 15% percentage in each group and is offset by a basically similar number of patients who had uncontrolled asthma in 2007 and whose asthma was controlled by 2010.

In terms of daily corticosteroid use, in 2007 there were statistically significant differences in favour of a lesser use of these drugs in the group who also received SIT (62% *vs.* 81%; p<0.01). These differences became more marked in 2010 (30 *vs.* 64%; p<0.01), with the SIT group only having a statistically significant reduced percentage of patients undergoing inhaled corticosteroid treatment 2007–2010 (p=0.03 in the SIT group *vs.* p>0.05 in the non-SIT group) (Figure 2).

In terms of secondary end-points (Table IV) we found that between 2007–2010, 10% of the SIT group patients and 20.6% of the non-SIT patients had had recourse once to A&E for asthma, with this difference non-significant (p>0.05). However, evaluating the number of trips to A&E showed that the SIT group patients who needed A&E needed it a mean 1.5 times over the course of the three

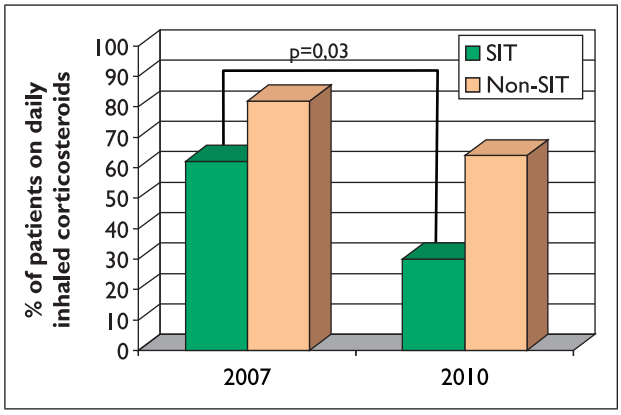


Figure 2. Patients taking daily inhaled corticosteroids in the two groups 2007–2010 (67 non-SIT and 29 SIT)

years, significantly less than the 3.16 times seen in the non-SIT patient group (p=0.02). Only one patient (in the non-SIT group) needed admission to hospital during this period.

Absenteeism from work was listed by around 10% of the SIT group patients and by 7% of the non-SIT group, again with this difference non-significant (p>0.05). Limitations to daily life was mentioned by 30 and 32% of patients in the SIT and non-SIT groups respectively, with this difference non-significant (p>0.05).

The use of inhaled rescue medication over the last year was low in both groups, and slightly lower in the SIT group, with this difference non-significant. Around half of the patients in both groups said they had no recourse to rescue medication in the last year and only 6–7% of patients in both groups had taken rescue medication more than once a week in the last year.

Turning to the use of systemic corticosteroids (via injection or in tablet form) over the last two years, it was seen that the patients who received SIT had significantly less recourse to this treatment (0% *vs.* 17%; p=0.03).

Table IV. Secondary end-points 2007-2010

	Non-SIT	SIT	p
Recourse to A&E for asthma (% of patients)	21%	10%	0,11
Mean recourse to A&E (in those patients who had recourse to it)	3,2	1,5	0,02
Hospital admission (n)	1	0	0,16
Absenteeism from work (% of patients)	7%	10%	0,35
Limitations to daily life (% of patients)	32%	30%	0,41
Relief medication use in the last year (% of patients)	52%	45%	0,37
Rescue medication use in the last year >1x/month (% of patients)	6%	7%	0,33
Systemic corticosteroid use in the last two years (% of patients)	17%	0%	0,03
Mean increase in percentage of body weight (2007 and 2010 comparison)	+3,9%	+3,2%	0,31
Self-reported diabetes (% of patients)	10%	0%	0,03
Self-reported high BP (% of patients)	32%	26%	0,29
Daily medication for high BP (% of patients)	30%	21%	0,23

SIT – specific immunotherapy; A&E – accident and emergency services; BP – blood pressure

It is also interesting that 10% of the asthma sufferers in the non-SIT group had diabetes and half of those took daily medication for this condition. None of the patients who had undergone SIT had diabetes, representing a significant difference in relation to the 10% in the group of asthmatics treated only with pharmacotherapy (p=0.03). Around 32% of the asthmatic patients who had not undergone SIT had high blood pressure, with 95% of these taking daily blood pressure medication. Around 26% of the patients in the SIT group had high blood pressure, with 80% taking treatment for it, with these differences not statistically significant (p>0.05).

A rise in mean body weight was seen in both groups, 3-4% over the 3 years. The non-SIT group had a mean weight gain from 71.6 to 74.4 kg (+3.9%): 30% maintained their initial weight ±1kg, 30% lost weight and 40% gained weight. The SIT group had a mean gain from 65.2 to 67.3 kg (+3.2%): 21% maintained their initial weight ±1kg, 34% lost weight and 45% gained weight.

It was seen that in both 2007 and 2010 the SIT patients had a mean lower weight than the non-SIT patients (p>0.05) with these differences not statistically significant.

DISCUSSION

In this work, dealing with a sample of asthmatic patients having hospital allergology and clinical immunology appointments, we found that after three years the level of asthma control previously attained was overall maintained, irrespective of the patients having received SIT in association with pharmacotherapy or not. This was shown by the minimum variation only seen in each group's mean ACT scores and by the majority of patients in both groups remaining at the same level of control and a similar percentage of patients who decreased or increased their level of control (Table II). That said, the SIT group had slightly higher ACT scores and significantly less patients not taking inhaled daily corticosteroids than the non-SIT group.

In 2007 the ACT scores were higher in the group who at this time had been undergoing SIT for under a year, but this did not mean that in the logistical regression undertaken for this study, SIT could be considered an independent factor associated to a better ACT score[6]. Just as in the 2007 study[6], we cannot now rule out that a better ACT score may be due to selection bias caused by the non-prescription of SIT to patients with more severe asthma. In 2010 the sample population re-analysed still showed differences which did not overall attain statistical significance, possibly due to the reduced sample size. That said, there was still bias in terms of both a greater representation of percentage of totally controlled patients (ACT=25) in the SIT group and a lesser percentage of non-controlled patients (ACT<20), which is around half the non-SIT group. We highlight that the percentage of atopic non-SIT group patients was similar in 2007 and 2010 (around 75%). In the 2007 study it was seen that atopy had no significant impact on the ACT score[6], the reason why in this work we did not perform a discriminative analysis of the ACT scores in the atopic and non-atopic patients.

While ACT is a very useful tool for evaluating asthma control, it was not the sole measurement used in this study. Other parameters such as consumption of corticosteroids, recourse to A&E and absenteeism from work were equally as important in a fuller evaluation of asthma control. Here we highlight that the SIT group had a marked drop in the percentage of patients taking daily inhaled corticosteroids: between 2007 and 2010 this percentage dropped to under half of the SIT group (from

62% to 30%) while the non-SIT group had only a decrease of approx. one fifth (from 81% to 64%). This was a statistically significant difference and a steroid-sparing effect in SIT. These results were similar to those seen in other studies[19-20], and this clearly shows that both in patients medicated with suitable pharmacotherapy and in patients medicated with drugs and undergoing SIT, asthma control can be maintained over time. The groups undergoing SIT had a much more marked reduction in doses of maintenance treatment, however, namely in doses of inhaled daily corticosteroids. They also had more significant immunological modifications – something we do not research into here – and better future long-term effects, even after SIT treatment ended[21-22].

We also highlight the significant differences seen in use of systemic corticosteroids: no patient in the SIT group had recourse to these over the last 2 years. This was also obviously related to the lesser recourse to A&E seen in these patients. SIT's efficacy was shown in the lesser number of non-scheduled medical appointments and the lesser use of control and relief medication seen in recently published studies into sublingual or subcutaneous immunotherapy[23,24].

Turning to weight, a raft of studies has shown an association between a high BMI and asthma severity. In our 2007 study, we found a BMI >30kg/m^2 to be a significant and independent risk factor for poor control of asthma, particularly in females[6]. We found here that in this adult asthmatic population there was a trend towards a mean weight increase in both the SIT+ pharmacotherapy group and the pharmacotherapy only group, but with no significant differences seen between them. There were also no differences seen in the weight gain among the patients who in 2010 were still taking daily corticosteroids and those who were not taking that medication.

While it is possible that the increase in BMI is related only to the aging process which occurred along the three years of the study in this adult population, this question of weight gain in asthmatics should be analysed in greater depth and prospectively in future studies. This is as not only can a higher BMI contribute to a lesser control of asthma, but also as despite a lack of secure evidence, it cannot be ruled out for certain that weight gain is exacerbated by the treatments administered.

We further add that in relation to the self-reported rate of diseases relatively common in our population such as diabetes and high blood pressure, there was more self-report of these pathologies and treatment for them in patient group treated with drugs only than in the group receiving SIT+pharmacotherapy. Only in the case of diabetes were the differences statistically significant, however.

Here it must obviously be considered that the differences in age seen between the two groups could in themselves account for the differences seen. We cannot draw any conclusion from these data which overall should work as an alert to stimulate analysis into the relationship between asthma and other very prevalent chronic diseases and in which asthma's chronic inflammation, particularly that in non-controlled asthma, can represent an important immunopathological factor. Here we draw attention to two recently published works. One, a prospective study, was a 10-year follow-up of around 38,000 40-year-old women and showed that asthma was associated with an increased risk of type II diabetes[25]. The other study showed glucose intolerance in asthma patients medicated only with beta-2-mimetic agents (to rule out any possible corticosteroid interference). The authors suggest that the chronic inflammation in asthma could induce insulin resistance and glucose intolerance, thus making it a risk factor for the onset of diabetes[26].

We would like to finish by underlining that this study has its limitations, particularly the small sample size and

that it is not a controlled and randomised study. What it sought to evaluate, however, using a slice-of-life study, was if the clinical practice of associating SIT to pharmacotherapy (a current strategy used by many allergologists) was associated with benefits in comparison to treatment with pharmacotherapy alone. Hence the reasons for the choice of treatment were not analysed in this study. In the face of the results presented here, we thus feel that this study, similarly to other national and international studies, shows yet again the clear existence of relevant clinical benefits to the specialised allergology and clinical immunology follow-up of patients with asthma, here shown by the obtaining and maintaining of good levels of asthma control over a 3-year period. Equally so, this study also suggests additional benefits are to be found in the judicious use of SIT, whose potential is shown in the financial savings and gains in quality of life attained.

CONCLUSIONS

Over 3 years, the majority of patients under specialised care maintained good levels of asthma control as measured by the ACT questionnaire, independently of being medicated with pharmacotherapy alone or pharmacotherapy plus SIT. The pharmacotherapy plus SIT group, however, had additional clinical improvements in other parameters, which could reflect SIT's relevant immuno-modulatory action, i.e. the significant reduction seen in use of inhaled corticosteroids, recourse to systemic corticosteroids and hospital A&E services.

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Annex 1 – Clinical questionnaire

1) In the last 3 years have you needed emergency treatment (after-hours clinic, emergency clinic, hospital A&E) because of asthma?
NO ☐ YES ☐
If YES, more or less how often in these 3 years ? _____

2) In the last 3 years have you been admitted to asthma because of asthma?
NO ☐ YES ☐
If YES, more or less how often in these 3 years? _____

3) In the last 3 years have you been absent from work or school because of asthma?
NO ☐ YES ☐
If YES, more or less how often in these 3 years? _____

4) Has asthma stopped you doing things you needed to do?
NO ☐ YES ☐
If YES, give examples of things asthma has stopped you doing
_____
_____
_____
_____

5) Are you taking DAILY medicine because of asthma?
NO ☐ YES ☐
If YES, which medicine?
_____
_____
_____
If YES, do you notice any difference if you forget to take these medications?
NO ☐ YES ☐

6) In the last year have you needed any relief treatment for asthma crises?
NO ☐ YES ☐
If YES, which relief medication for asthma?
_____
_____
If YES, more or less how often have you taken it over the course of the year?
1-2 times per year ☐ 3-10 times per year ☐
1-2 times per month ☐ 1-2 times per week ☐
1 time per day ☐ More than 1 time per day ☐

7) In the last two years have you needed to take cortisone tablets or injections because of asthma?
NO ☐ YES ☐
If YES, more or less how often have you taken cortisone in the last 2 years? _____

8) Do you have high blood pressure?
NO ☐ YES ☐
If YES, do you have to take medication for this?
NO ☐ YES ☐

9) Do you have diabetes?
NO ☐ YES ☐
If YES, do you have to take medication for this?
NO ☐ YES ☐

10) Please tell us your current weight and height:
Weight: _____ Kg Height: _____ metres