Quality of life relates to glucocorticoid treatment regimen, adiposity and insulin resistance in adults with congenital adrenal hyperplasia: United Kingdom Congenital adrenal Hyperplasia Adult Study Executive (CaHASE)

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BACKGROUND

Quality of life (QoL) has been variously reported as normal or impaired in adults with congenital adrenal hyperplasia (CAH). To explore the reasons for this discrepancy we investigated the relationship between QoL, glucocorticoid treatment and other health outcomes in CAH adults.

METHODS

Patient recruitment

The CaHASE cohort is a cross-sectional prospective study of CAH adults recruited from 17 specialized British Endocrine centres. The study protocol was approved by West Midlands (MREC/03/7/086) and registered with ClinicalTrials.gov (NCT00749593).

All centres contacted adult patients (18 years or older) with a confirmed diagnosis of CAH currently under their care. Recruitment started August 2004 and ended July 2007. All participants gave written informed consent .

Outcome measures

Clinical and drug history and examination.

Waist circumference, weight and height (BMI).

Systolic and diastolic BP, bone mineral density.

Triglycerides and HDL cholesterol, glucose and insulin (HOMA-IR).

Androstenedione, 17-OHP, testosterone.

QoL: SF-36 questionnaires.

Biochemistry measurements

Performed at local laboratories (all participate in the UK NEQAS scheme for quality control of steroid immunoassays) Serum insulin was measured centrally using an ultrasensitive enzyme-linked immunosorbent assay (DRG instruments, Marburg, Germany).

Mutation analysis, mutation groups and *in vitro* analysis of *CYP21A2* mutations

CYP21A2 gene deletion and chimeric genes were detected using a commercially available multiplex-ligation probe amplification (MLPA) strategy following the manufacturers protocol (mrc-Holland, Amsterdam, The Netherlands). Pseudogene-derived CYP21A2 point mutations were performed by targeted multiplex-mini sequencing after allele specific PCR amplification of the CYP21A2 gene. If no common mutations were detected, direct DNA sequencing of the entire CYP21A2 gene was performed.

Patients were categorized into established CYP21A2 mutation groups according to their genotype with the less severe mutation determining the group: Null (mutations absent *in vitro* activity), A (intron 2 splice site mutation), B (mutations such as the I172N mutation and mutations with 1-10% *in vitro* residual enzyme activity), C (mutations such as P30L, V281L, and P453S or above 20-30% *in vitro* 21-hydroxylase activity).

Data analysis

Cross-sectional analysis of 151 adults with 21-hydroxylase deficiency (50M: 47 with classic and 3 with non-classic CAH; 101F: 75 with classic and 26 with non-classic CAH) aged 18-69 years in whom QoL (SF-36), glucocorticoid regimen, anthropometric and metabolic measures were recorded. Relationships were examined between QoL, type of glucocorticoid (hydrocortisone, prednisolone and dexamethasone), and dose of glucocorticoid expressed as prednisolone dose equivalent (PreDEq). QoL was expressed as z-scores calculated from matched controls (14,430 subjects from UK population, courtesy of Professor John Brazier, Sheffield University). Principal components analysis (PCA) was undertaken to identify clusters of associated clinical and biochemical features and the principal component (PC) scores used in regression analysis as predictor of QoL.

RESULTS

QoL scores were associated with type of glucocorticoid treatment for vitality (P = 0.002) and mental health (P = 0.011), with higher z-scores indicating better QoL in patients on hydrocortisone than in patients receiving prednisolone or dexamethasone (P <0.05). QoL did not relate to PreDEq or mutation severity. PCA identified three PCs (PC1, *disease control*; PC2, *adiposity and insulin resistance*; PC3, *blood pressure and mutations*) that explained 61% of the variance in observed variables. Stepwise multiple regression analysis demonstrated that PC2 (comprising waist circumference, serum triglycerides, HOMA-IR and HDL-cholesterol) was associated with QoL scores, specifically impaired physical functioning, bodily pain, general health, Physical Component Summary Score (P < 0.001) and vitality (P = 0.002).

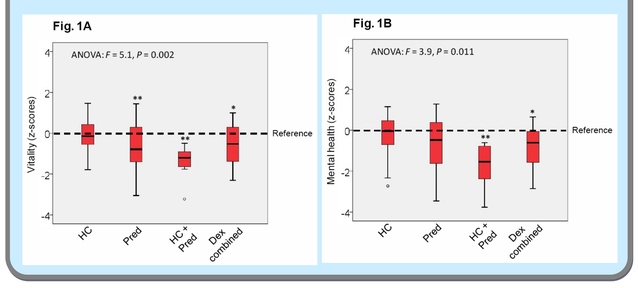
Table 1. Quality of life SF-36 standardized scores and z-scores for CAH adults, based on reference data obtained from Professor John Brazier (University of Sheffield, UK) constructed a representative random sample of 14,430 subjects from the UK population aged 18 to 79 years. For every CAH patient, twenty sex- and age-matched controls were randomly selected from the representative reference samples and z-scores generated. Adjustment for age and sex was performed by transformation of all domain score values from patients into age- (decade) and sex-adjusted z-scores. Red = Physical health domains; Blue = Mental health domains.

	Standardized scores	Z-scores
	Mean ±SD	Mean ±SD
Physical function	81.2 ±25.2	-0.74 ±1.53
Role limitations due to physical problems	74.2 ±37.7	-0.71 ±1.33
Bodily pain	68.4 ±27.8	-0.45 ±1.26
General health	56.1 ±25.4	-0.61 ±1.09
Vitality	50.4 ±21.6	-0.87 ±1.21
Social functioning	73.2 ±26.9	-0.54 ±1.02
Role limitations due to emotional problems	69.3 ±40.1	-0.91 ±1.66
Mental health	65.9 ±20.9	-0.718 ±1.19

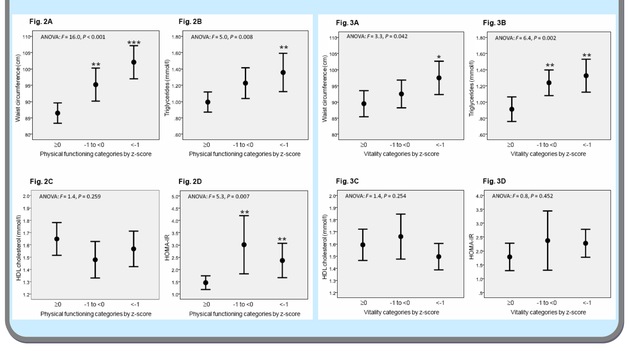
Table 2. Regression coefficients (β) and explained variances obtained from stepwise multiple regression analysis using the three principal components (PC1, PC2 and PC3) as predictor variables and health related QoL SF-36 questionnaire, age- and sex-adjusted, z-scores as dependent variables. Only PC2, reflecting ***adiposity and insulin resistance*** **(waist circumference, serum triglycerides, HOMA-IR and HDL-cholesterol)** was retained showing adverse relationships with physical function, bodily pain, general health, vitality and Physical Component Summary Score. Additional adjustment for PreDEq, or type of glucocorticoid replacement (hydrocortisone, prednisolone and dexamethasone) did not change these relationships. Red = Physical health domains; Blue = Mental health domains.

	Predictor variable		
Dependent variables	β (95% CI)	P	r^2 (%)
Physical function	-0.72 (-1.11 to -0.35)	<0.001	19.9
Role limitations due to physical problems	Not significant	---	---
Bodily pain	-0.55 (-0.82 to -0.28)	<0.001	21.6
General health	-0.50 (-0.80 to -0.20)	0.001	16.0
Physical Component Summary Score	-0.58 (-0.83 to -0.33)	<0.001	26.4
Vitality	-0.40 (-0.65 to -0.16)	0.002	15.5
Social functioning	Not significant	---	---
Role limitations due to emotional problems	Not significant	---	---
Mental health	Not significant	---	---
Mental Component Summary Score	Not significant	---	---

Fig 1. Influence of type of glucocorticoid on QoL: Boxplots representing median and interquartile ranges of QoL (SF-36) z-scores of the two quality of life domains, vitality (A) and mental health (B), for CAH patients using different type of glucocorticoid treatment; whiskers represent the 5th and 95th percentiles. A z-score of 0 represents the median of the reference population. *Post hoc* analysis: compared with hydrocortisone treated patients, z-scores for vitality and mental health were **lower** in those treated with a combination of hydrocortisone plus prednisolone (**P <0.01) or any dexamethasone combination (*P <0.05) or prednisolone (**P <0.01, for vitality only). HC = hydrocortisone, Pred = prednisolone, Dex = dexamethasone.



Influence of individual components of the *adiposity and insulin resistance* on physical functioning (Fig. 2) and on vitality QoL (Fig. 3): Error plots with mean and 95% confidence limits showing the size of waist circumference (A), levels of triglycerides (B) and HDL cholesterol (C), and HOMA-IR (D) according to the physical functioning (Fig. 1) or vitality (Fig. 2) domain categorized into three groups based on z-scores ≥0 (n = 69), <0 to -1 (n = 36) and <-1 (n = 46). *Post hoc* analysis: *P <0.05, **P <0.01, ***P <0.001 compared to group with z-score ≥0.



SUMMARY OF FINDINGS IN ADULT CAH PATIENTS

- **QoL was impaired in this cohort of patients.**
- **QoL was better in patients taking hydrocortisone treatment alone compared to those taking either prednisolone or dexamethasone treatment.**
- **Increased adiposity and Insulin resistance were associated with impaired QoL, predominantly in the physical health domains.**

CONCLUSIONS

Increased adiposity and insulin resistance, and use of prednisolone or dexamethasone, are associated with impaired QoL in adults with CAH. Further studies are justified to establish whether optimising the choice of glucocorticoid treatment and/or weight loss can improve QoL in this disadvantaged patient group.

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