Reproductive BioMedicine Online (2013) 26, 62–67

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ARTICLE

Intrafollicular soluble receptor for advanced glycation end products (sRAGE) and embryo quality in assisted reproduction

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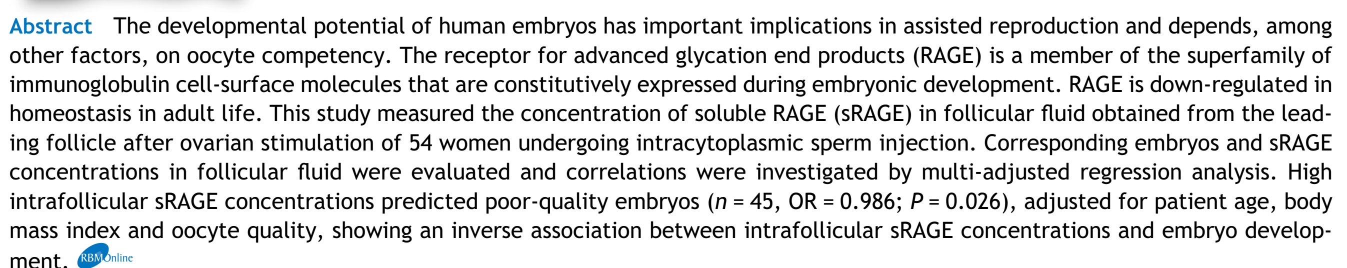

Abstract The developmental potential of human embryos has important implications in assisted reproduction and depends, among other factors, on oocyte competency. The receptor for advanced glycation end products (RAGE) is a member of the superfamily of immunoglobulin cell-surface molecules that are constitutively expressed during embryonic development. RAGE is down-regulated in homeostasis in adult life. This study measured the concentration of soluble RAGE (sRAGE) in follicular fluid obtained from the leading follicle after ovarian stimulation of 54 women undergoing intracytoplasmic sperm injection. Corresponding embryos and sRAGE concentrations in follicular fluid were evaluated and correlations were investigated by multi-adjusted regression analysis. High intrafollicular sRAGE concentrations predicted poor-quality embryos (n = 45, OR = 0.986; P = 0.026), adjusted for patient age, body mass index and oocyte quality, showing an inverse association between intrafollicular sRAGE concentrations and embryo development.

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KEYWORDS: embryo quality, follicular fluid, ICSI, sRAGE

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http://dx.doi.org/10.1016/j.rbmo.2012.10.001

Introduction

Glycation is the non-enzymic addition of sugars to proteins and lipids. Advanced glycation end products (AGE) are a heterogeneous group of non-enzymically modified proteins. Protein glycation was originally thought to tag senescent proteins for degradation by macrophages. Also, defective clearance of AGE-modified proteins was believed to increase with ageing, and accelerated AGE formation occurs in diabetes and atherosclerosis (Vlassara et al., 1992).

The receptor for advanced glycation end products (RAGE) is a member of the immunoglobulin superfamily located in the membranes of immune, endothelial, epithelial and central nervous system cells (Schmidt et al., 2000). Binding of AGE to RAGE triggers signalling of the MAP kinase and NF-κB pathways (Bucciarelli et al., 2002), and glycation is responsible, via RAGE, for increased oxidative stress and inflammation caused by the formation of reactive oxygen species. RAGE is frequently associated with pro-inflammatory responses in which AGE, the ligands of RAGE, accumulate and may contribute to immune disorders, cardiovascular diseases, diabetes, Alzheimer's disease and cancer. In addition to activating pro-inflammatory responses, increased RAGE concentrations down-regulate cellular defence mechanisms (Bierhaus et al., 2005).

RAGE is constitutively expressed during embryonic development; however, it is down-regulated in adult life except in the skin and lungs (Brett et al., 1993). Thus, RAGE is usually expressed at low levels during homeostasis (Neeper et al., 1992), but its expression increases in diseases characterized by the up-regulation and accumulation of its ligands, namely AGE. In numerous cell types, the main mechanism of RAGE action is through changes in signal transduction induced after AGE binding (Ramasamy et al., 2009).

A circulating soluble isoform of RAGE (sRAGE) has been identified in humans. This isoform contains the extracellular domain of RAGE but is missing the cytosolic and transmembrane domains. sRAGE is believed to act as a decoy that binds to pro-inflammatory ligands and prevents their access to the cell membrane (Hudson et al., 2008). In addition to the relationship between sRAGE and pro-inflammatory diseases (Maillard-Lefebvre et al., 2009), sRAGE serum concentrations have been associated with both physiological and pathological states during pregnancy, such as preterm labour and pre-eclampsia (Germanova et al., 2010).

Both soluble and intact forms of RAGE have been studied in polycystic ovarian syndrome (PCOS). Higher serum concentrations of AGE and of full-length RAGE were found in young normoglycaemic PCOS patients relative to healthy controls (Diamanti-Kandarakis et al., 2005). The same group has demonstrated that AGE and RAGE expression was higher in PCOS than normal ovarian tissue; AGE was localized in the follicular cell layers (i.e. the granulosa and theca layers) and luteinized cells, and RAGE stains were more pronounced in granulosa cells, theca interna, endothelial and stromal cells on PCOS patients (Diamanti-Kandarakis et al., 2007).

sRAGE concentrations in the follicular fluid of assisted reproduction patients were higher in women who had successful pregnancies following IVF relative to those who did not conceive. However, serum sRAGE concentrations showed a negative correlation with the number of stimulated follicles and retrieved oocytes (Malickova et al., 2010). Fujii and Nakayama (2010) studied AGE, sRAGE and vascular endothelial growth factor (VEGF) in plasma and follicular fluid of patients undergoing IVF as a function of patient age. Follicular VEGF was higher in older patients, but follicular sRAGE was not significantly different in young or older women. The authors suggested a correlation between the regulation of RAGE–VEGF and reproductive dysfunction in ageing women (Fujii and Nakayama, 2010).

Recently, other investigators have evaluated AGE (e.g. toxic AGE, pentosidine and carboxymethyl lysine) in blood and follicular fluid of patients undergoing assisted reproduction treatment and observed that accumulation of intrafollicular pentosidine (a product of AGE) was highly correlated with poor follicular and embryonic development and a lower probability of a pregnancy (Jinno et al., 2011).

The aforementioned studies have established that sRAGE has a role in the follicular environment and that higher sRAGE but lower AGE concentrations could be associated with better IVF outcomes. There are no studies regarding intrafollicular sRAGE and its connection to embryo development. The aim of the present study was to measure sRAGE concentrations in follicular fluid samples obtained from leading follicles of women undergoing intracytoplasmic sperm injection (ICSI) cycles and test whether sRAGE concentrations correlated with the quality of the corresponding oocytes and embryos.

Materials and methods

Patients

This study was approved by the Ethics Committee of the Federal University of Sao Paulo (protocol 1699/06, 15 June 2007) and informed consent was obtained from all participants. Between January 2007 and December 2008, 132 patients undergoing ICSI cycles at the Fertility-Assisted Fertilization Centre, Sao Paulo, Brazil, were prospectively enrolled. Inclusion criteria were presence of both ovaries, regular menstrual cycles, body mass index (BMI) lower than 35 kg/m^2, no current infectious diseases, no uterine pathology, basal FSH less than 14 IU/l and basal oestradiol less than 70 pg/ml. Exclusion criteria were male partners presenting with severe oligozoospermia or azoospermia. Because some studies suggested that endometriosis (Sharma et al., 2010) and PCOS (Ramasamy et al., 2009) may affect sRAGE concentrations, this study also excluded patients diagnosed with those pathologies. After all the exclusion criteria had been applied, 54 patients qualified to participate in this study (**Figure 1**).

IVF procedure

Pituitary blockage was obtained with a gonadotrophin-releasing hormone (GnRH) agonist (Lupron; Abbot SA Societé Française des Laboratories, France) (67.6% of the participants) or a GnRH antagonist (Cetrotide; Serono, Switzerland) (32.4% of the participants). Ovarian stimulation was accomplished using recombinant FSH (Gonal-F; Serono, Switzerland). When at least two follicles reached a diameter of 16 mm, follicular maturation was triggered

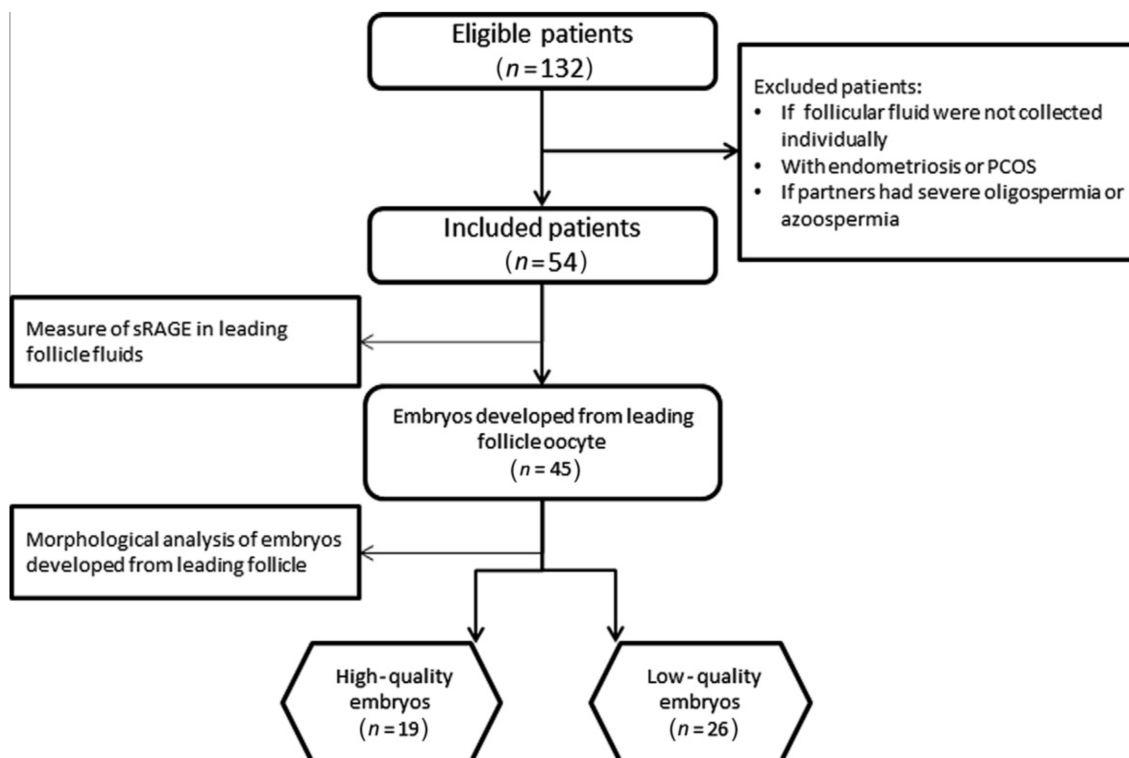

Figure 1 Flow diagram of the study.

with an injection of 250 μg recombinant human chorionic gonadotrophin (Ovidrel; Serono). Oocyte retrieval was performed after 35–36 h by transvaginal ultrasound-guided aspiration; the luteal phase was supported by 90 mg of daily progesterone (Crinone; Serono) administered vaginally. All of the oocytes were fertilized by ICSI (Palermo et al., 1992).

Sample collection and analysis

During oocyte retrieval, the monofollicular fluid from the leading follicle was aspirated and collected. No flushing procedures were performed during oocyte retrieval. The follicular fluid samples were centrifuged for 10 min at 800*g* to separate red blood cells, leukocytes, granulosa cells and debris. The supernatants were frozen without preservatives and stored at −80°C until assayed. The samples were analysed at the molecular gynaecology laboratory of the gynaecology department of the Federal University of Sao Paulo.

The follicular fluid samples were analysed for sRAGE using Luminex xMAP technology (MILLIPLEX MAP Human Soluble Cytokine Receptor Panel; Merck-Millipore, USA) according to the manufacturer's protocol; the detection limit was 5.0 pg/ml. Due to volume variability among follicles, sRAGE concentrations were adjusted to protein content, as reported elsewhere (Fanchin et al., 2007; Franchimont et al., 1989). Protein concentrations were measured by automated photometry analysis (Cobas C-111 Analyser; Roche Diagnostics, Switzerland). The mean concentration of intrafollicular protein was 5.0 g/dl, and sRAGE concentrations were expressed as ng/g protein).

Patient serum was collected at oocyte retrieval and the concentrations of FSH, oestradiol and progesterone were determined by an automated multi-analysis system using chemiluminescence (Advia Centaur; Siemens). Anti-Müllerian hormone and inhibin-β were measured by ELISA kits (Diagnostic System Laboratories, Webster, Texas, USA). Hormone measurements and clinical data of all patients were annotated (i.e. age, BMI and infertility factors) and analysed.

Statistical analysis

Data analyses were performed using the Statistical Package for Social Sciences version 18 (SPSS, USA). Patient demographic data were evaluated using descriptive statistics, which included information on means and frequencies. Continuous variables were compared using mean comparison tests and correlation and regression analyses were used to evaluate the relationships between variables.

The normal fertilized oocytes were those metaphase II (MII) oocytes injected that showed two pronuclei during the fertilization checking process. Embryo quality was evaluated on the transfer day (e.g. day 2 or 3 of development). High-quality embryos were those that developed out of the MII oocytes that presented at least four blastomeres on day 2, or at least six regular blastomeres on day 3, showed <20% fragmentation and had no multinucleation or dominant blastomeres. Implantation rate was calculated as the number of gestational sacs per number of embryos transferred. Clinical pregnancy was defined as the presence of a gestational sac with a heartbeat, visualized via ultrasound 5–6 weeks after embryo transfer. Pregnancy rate was calculated as the number of pregnant patients per number of patients with embryos transferred.

From the fertilized oocytes, 45 embryos developed and were analysed for morphological characteristics. Continuous variables, presented as mean ± standard deviation (SD) were compared using Student's t-test. Linear associations were assessed by the correlation coefficient. Multiple logistic regression models were used to assess the impact of the independent variable (sRAGE concentrations) on the respective embryo quality (high- and low-quality embryos). Potential explanatory variables included in the model were patient age, BMI and oocyte quality. The results were reported as odds ratios and associated *P*-value. *P*-values ≤ 0.05 were considered to be statistically significant.

Factors examined in the multivariate models included patient age and BMI, and the results were reported as odds ratios and *P*-value. We considered *P*-values ≤ 0.05 to be statistically significant.

In order to evaluate the statistical power of this study, the statistical power was calculated based on intrafollicular mean sRAGE concentrations according to groups of high- or low-quality embryos. The power to identify differences in RAGE concentrations in those groups is 89.3%.

Results

The general characteristics of patients and outcomes of ICSI cycles are shown in **Table 1**. Infertility was categorized as idiopathic infertility (44.4%), male infertility (27.8%), ovarian factor of infertility (16.7%), tubal obstruction (5.6%) and male- and female-associated factors (5.6%).

All oocytes collected from the leading follicle were in MII stage and were fertilized by ICSI (normal fertilization rate: 39 2PN/54 oocytes from leading follicle, 72.2%). The mean sRAGE concentration in the follicular fluid was 242.9 ± 185.8 ng/g protein. There are no differences in sRAGE concentrations between patients who received GnRH agonist or antagonist for pituitary blockage.

Intrafollicular sRAGE concentrations were inversely correlated with BMI (Pearson correlation $r = -0.379$; $P = 0.011$) and oocyte quality (Pearson correlation $r = -0.315$; $P = 0.045$). The association of intrafollicular sRAGE concentrations with high-quality embryos was tested by multinomial logistic regression and was adjusted for patient age, BMI and oocyte quality, as these variables can be potential confounders of this association. The regression model showed that intrafollicular sRAGE concentrations predicted an inferior quality of embryos independently of the patient age, BMI and oocyte quality (**Table 2**). The recombinant FSH dose or the number of oocytes collected did not correlate with sRAGE concentrations (Pearson correlation $r = 0.200$ and $r = 0.095$, respectively) or embryo quality (Pearson correlation $r = -0.161$ and $r = -0.003$).

Moreover, the mean concentration of intrafollicular sRAGE was strikingly lower in high-quality embryos ($n = 19$, 152.8 ± 24.5 ng/g protein) than poor-quality embryos ($n = 26$, 295.8 ± 45.2 ng/g protein, $P = 0.008$). There was no association between the serum hormones measured on retrieval day and embryo quality or sRAGE concentrations.

Table 1 Demographic and clinical data of the 54 patients studied.

Variable	*Sample*
Age (years)	33.7 ± 4.8
BMI (kg/m^2)	22.9 ± 2.7
Total FSH administered (IU)	2291.5 ± 681.2
No. of oocytes recovered	13.7 ± 8.0
MII oocyte rate	523/739 (70.8)
Normal fertilization rate	329/460 (71.5)
Good-quality embryo rate	217/329 (66.0)
No. of embryos transferred per patient	2.6 ± 0.9
Implantation rate	30/133 (22.6)
Biochemical pregnancy rate	19/51 (37.3)
Clinical pregnancy rate	15/51 (29.4)

Values are mean ± SD or *n*/total (%).

Table 2 Multinomial logistic regression analysis of intrafollicular sRAGE concentrations from 45 embryos.

	Odds ratio	*P-value*
Constant	480.7	NS
sRAGE concentration (ng/g protein)	0.986	0.026
Age (years)	1.128	NS
BMI (kg/m^2)	0.714	NS
Oocyte quality	1.029	NS

NS = not statistically significant; sRAGE = soluble receptor for advanced glycation end products.

Discussion

The main goal of IVF programmes is to obtain a number of developmentally competent oocytes and high-quality embryos and improve the chances of a healthy baby. The follicular fluid, which derives from blood constituents transposed through the follicular barrier and from substances secreted by follicular cells, provides the microenvironment for the proper growth and maturation of oocytes. A complex mixture of factors present in the follicular fluid contribute to and also reflect the potential for oocyte growth and development (Driancourt and Thuel, 1998; Revelli et al., 2009).

The present study measured sRAGE concentrations in samples from individual follicles to determine if there was a correlation with the quality of the ensuing embryos. Pregnancy rates were not included in the analysis since not all of the embryos tested were transferred and the majority of patients received multiple embryos. sRAGE concentrations were inversely associated to high-quality embryos, but the mechanism underlining this association remains unclear.

Other studies have found an inverse association between circulating sRAGE concentrations in cardiovascular diseases (Park et al., 2011) and hypertension (Geroldi et al., 2005), and a positive association with diabetes (Ramasamy et al., 2011), chronic kidney disease (D'Agati and Schmidt, 2010) and pre-eclampsia (Oliver et al., 2011). A positive relationship between serum sRAGE and PCOS has been reported (Diamanti-Kandarakis et al., 2008), and association of higher RAGE gene expression and endometriosis had been demonstrated as well (Sharma et al., 2010). The current study has excluded endometriosis or PCOS patients.

Previous studies of IVF patients have found an inverse association between serum sRAGE concentrations and age (Fujii and Nakayama, 2010) and a positive relationship between intrafollicular sRAGE concentrations and clinical outcomes (Malickova et al., 2010). Since RAGE is produced in response to AGE, the findings showed by Jinno et al. (2011) support the current results, as they reported that accumulation of intrafollicular pentosidine (a product of AGE) was highly correlated with poor follicular and embryonic development and a lower likelihood of pregnancy. The current findings and those by Jinno et al. (2011) together would suggest high sRAGE concentrations associated with lower embryo quality would reflect high AGE accumulation and consequently sRAGE synthesis.

On the other hand, since RAGE to AGE binding triggers cellular signalling, generate reactive oxygen species and pro-inflammatory mediators, it is supposed that if sRAGE acts as a decoy for ligands of RAGE, high sRAGE protect cells from the deleterious effects of ligand-RAGE activity (Santilli et al., 2009). Thus, higher intrafollicular sRAGE should protect the oocyte from reactive oxygen species via inhibition of the ligand-RAGE activation of down-stream signalling, which is opposite to the current observations. Another way to explain this apparent controversy is that folliculogenesis constitutes an inflammatory episode where large quantities of numerous cytokines are produced and secreted into the follicular fluid. Follicles produced during the hyperstimulated cycles are in a highly inflammatory environment, and there are 10-times higher concentrations of secreted cytokines than in follicles of non-stimulated cycles (Runesson et al., 2000). Such an extremely inflammatory environment could trigger an immense production of AGE and the deleterious consequences of ligand-RAGE activity on oocyte quality, including the adverse clinical events reported (Jinno et al., 2011). A lot remains to define the exact biological role of sRAGE (Santilli et al., 2009).

This multiple regression model revealed an inverse association of sRAGE with embryo quality that was independent of age, BMI and oocyte quality. But sRAGE was also inversely correlated to oocyte quality and BMI. Although elevated sRAGE concentrations seem to also negatively affect oocyte quality, the effect was not significant when adjusted to patient age and BMI (data not shown). Norata et al. (2009) observed that plasma sRAGE were negatively correlated with BMI, waist/hip circumference and fasting glycaemia, supporting the possible involvement of sRAGE with metabolic processes, even in patients without metabolic diseases.

In spite of the high oestrogen concentrations in patients undergoing ovarian stimulation, this study did not observe any correlation between serum oestrogen and intrafollicular sRAGE concentrations. Earlier in-vitro studies showed that 17β-oestradiol stimulated RAGE expression in endothelial cells in an oestrogen receptor-dependent transcriptional process (Tanaka et al., 2000; Mukherjee et al., 2005). Prescribed oestrogens may help maintain the RAGE-signalling events in post-menopausal women (Mukhopadhyay and Mukherjee, 2005).

The study of follicular fluid from individual leading follicles allowed the comparison of sRAGE concentrations in the corresponding oocytes and the assessment of relationship to embryo quality. One limitation is that evaluate all follicles and the corresponding embryos from each patient could be evaluated, but only the leading follicle; such a comprehensive study was not feasible within the time restrictions of an IVF centre. A second limitation is that implantation rate and clinical pregnancy could not be linked to follicular sRAGE concentrations, as embryos derived from the leading follicles were not always transferred or multiple embryos were transferred.

In summary, the findings suggest an association between intrafollicular concentrations of sRAGE and poor embryo quality. However, further research in this field is required to elucidate the function of the AGE–RAGE network in stimulated cycles for IVF.

Acknowledgements

The authors gratefully acknowledge the assistance in sample collection of the IVF laboratory team in the Fertility-Assisted Fertilization Centre, São Paulo, Brazil, and the researchers at the Central Laboratory of Sao Paulo Hospital – Federal University of São Paulo, São Paulo, Brazil, for their assistance with the Luminex xMAP technology. They also thank John CM Tsibris, PhD, University of South Florida, Tampa FL, USA, for reading the manuscript and stimulating discussions. This study was supported by the São Paulo Research Foundation (FAPESP; Grant 2007/58467-0) and the National Council for Scientific and Technological Development of Brazil (CNPq; Grant 579224/2008-2).

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Declaration: The authors report no financial or commercial conflicts of interest.

Received 12 July 2012; refereed 21 September 2012; accepted 2 October 2012.